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<b>(21) International Application Number:</b> PCT/US98/23161 <b>(22) International Filing Date:</b> 30 October 1998 (30.10.98)  <b>(30) Priority Data:</b> 08/985,809      5 December 1997 (05.12.97)      US  <b>(71) Applicant (for all designated States except US):</b> LOYOLA UNIVERSITY OF CHICAGO [US/US]; 2160 South First Avenue, Maywood, IL 60153 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> PEREZ-REYES, Edward [US/US]; 320 South Birchwood Drive, Naperville, IL 60540 (US). CRIBBS, Leanne, L. [US/US]; 1737 North Natoma, Chicago, IL 60707 (US).  <b>(74) Agents:</b> HEFNER, M., Daniel et al.; Leydig, Voit & Mayer, Ltd., Suite 4900, Two Prudential Plaza, 180 North Stetson, Chicago, IL 60601-6780 (US).			<b>(81) Designated States:</b> CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF USING SAME			
<b>(57) Abstract</b>  The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel and cells and cell lines expressing such nucleic acids. The present invention also provides an isolated or substantially purified T-type calcium channel and an isolated or substantially purified antibody molecule recognizing an epitope on a T-type calcium channel protein.			

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## T-TYPE VOLTAGE-GATED CALCIUM CHANNELS AND METHOD OF USING SAME

### STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

This invention was made with Government support under Grant Number HL58728 awarded by the National Heart, Lung, and Blood Institute of the National Institutes of Health. The United States Government may have certain rights in this invention.

### TECHNICAL FIELD OF THE INVENTION

The present invention relates to cloned T-type calcium channels.

### BACKGROUND OF THE INVENTION

Biological membranes are themselves generally impermeable to ionic species. Thus, ions enter cells through regulated pores formed from membrane-associated proteins. Most of these regulated pores are voltage-dependent and are thus able to transduce changes in the transmembrane potential into ion flux. Voltage-gated ion channels form a "superfamily" of related proteins (cf. Jan et al., *Nature*, 345, 672 (1990)). Peculiar to this genus is a high degree of conservation in molecular structure. Generally, voltage-gated channels are membrane bound glycosylated proteins formed of many subunits. Large  $\alpha$  subunits form a pore in the membrane that is selective for a given ionic species. Each  $\alpha$  subunit contains four domains (I, II, III, and IV). Each channel domain has six putative transmembrane helical segments ( $S_1$ - $S_6$ ). In general, the segments within each domain are similar but not identical. Aside from overall structural conservation, certain charged residues within the domains are highly conserved among voltage-gated ion channels (Jan et al., *supra*; Stühmer et al., *Nature*, 339, 597-603 (1989)).

Differences in charged residues between groups of voltage-gated ion channels confer properties unique to each subgroup, such as ion selectivity. For example, most voltage gated ion channels are selective for either sodium, potassium or calcium. Known calcium channels require a ring of negative charge provided by glutamate residues found at similar locations in each of the domains (Yang et al., *Nature*, 366, 158-61 (1993)).

Voltage-gated channels are often classified on the basis of their electrophysiology. The resting membrane potential of most animal cells is between about -70 mV and -80 mV. When the membrane becomes depolarized (moved towards 0 mV), various membrane channels become activated (they are said to

“open”). Thus, one basis for classifying membrane channels is the membrane potential necessary to activate (or “gate”) them (voltage dependency). For example, “T-type” calcium channels are activated at a lower voltage than L- or N-type channels (Nowycky et al., *Nature*, 316, 440-43 (1985)). Other physiological properties are the activation kinetics, inactivation kinetics, tail current (deactivation kinetics), and single channel conductance. Thus, in comparison to other calcium currents, T-type calcium current is characteristically short (Chen et al., *J. Gen. Physiol.*, 96, 603-30 (1990)), and it exhibits characteristically slow activation kinetics near threshold, fast inactivation kinetics, and slow tail current (Randall et al., *Neuropharmacol.*, 63, 879-93 (1997); Carbone et al., *Nature*, 310, 501-02 (1984); Nilius et al., *Nature*, 316, 443-46 (1985)).

Calcium currents have been implicated in many neurological and muscular functions. For example, T-type calcium current is associated with cardiac pacemaker activity, pain transmission in the central nervous system, and in other physiological functions. Defects in T-type calcium current have been implicated in cardiac arrhythmia, hypertension, and epilepsy. Given their potential clinical value, the pharmacological properties of calcium channels have been the subject of extensive study. Most such studies have involved L-type channels because, unlike T-type channels, L-type calcium channels are readily purified from cell extracts. For example, L-type calcium channels have been purified using dihydropyridine drugs (e.g., nifedipine) which can bind with sufficiently high affinity to serve as a ligand for purifying L-type calcium channels. Such purified and cloned L-type calcium channels have been used to develop assays for drugs affecting L-type calcium channels (see, e.g., U.S. Patents 5,429,921 and 5,386,025).

While many electrophysiological characteristics of T-type calcium currents are known, the lack of isolated T-type channels has stalled research into the pharmacology and biophysics underlying the T-type calcium current, at least in comparison with other calcium channels. Indeed, while it is generally assumed that voltage-sensitive ion channels are responsible for the current, no such channel protein, nor any nucleic acid encoding such a protein, has been isolated. In view of the foregoing problems, there exists a need for an isolated T-type calcium channel and a nucleic acid encoding a T-type calcium channel.

### BRIEF SUMMARY OF THE INVENTION

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel and cells and cell lines expressing such nucleic acids. The present invention also provides an isolated or substantially purified T-type calcium channel and an isolated or



substantially purified antibody molecule recognizing an epitope on a T-type calcium channel protein.

The present invention is useful for exploring the electrophysiology and pharmacology of the T-type calcium current. Such knowledge can lead to the development of drugs for potentiating or attenuating T-type calcium channels. Thus, the present invention provides an assay for identifying potential drugs affecting T-type calcium channels by exposing cells expressing a T-type calcium channel to a putative drug and then measuring the calcium flux in response to a change in membrane potential. The identification of drugs affecting T-type calcium channels will facilitate even greater understanding of the biophysics of these proteins. Furthermore, some such drugs could have potential clinical applications.

The invention can best be understood with reference to the accompanying drawings and in the following detailed description of the preferred embodiments.

### BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1E compare the complete amino acid sequences of three types of T-type calcium channels ( $\alpha 1G$  (or Ca<sub>v</sub>T.1),  $\alpha 1H$  (or Ca<sub>v</sub>T.2), and  $\alpha 1I$  (or Ca<sub>v</sub>T.3)), indicating conserved functional domains.

Figures 2A-2D are graphic representations of the current-voltage relationships of three cloned T-type calcium channels (Figures 2A, 2B, and 2C) and a cloned R-type calcium channel (Figure 2D).

Figure 3A is a graphic representation of the average current-voltage curve for cloned T-type calcium channels ( $\alpha 1G$ , triangles,  $\alpha 1H$ , inverted triangles,  $\alpha 1I$ , circles), and a cloned R-type calcium channel (filled squares). Figure 3B compares the normalized conductance of a cloned T-type calcium channel at three different concentrations of BaCl<sub>2</sub>.

Figure 4 depicts average kinetics of the tail current as a function of repolarization potential for  $\alpha 1G$  (triangles),  $\alpha 1H$  (inverted triangles),  $\alpha 1I$  (circles), and a cloned R-type calcium channel (filled squares).

Figures 5A and 5B graphically present data concerning the use of a cloned T-type calcium channel to detect drugs affecting the channel. Figure 6A depicts the effect of 100  $\mu M$  on current-voltage relationships with a single dosage of mibefradil. Figure 6B illustrates the effect on T-type channel conductance of various doses of mibefradil.

### DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides an isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel  $\alpha$

subunit. The nucleic acid can be of any type, and it can include other elements aside from a sequence encoding a T-type calcium channel domain or domains. For example, where the nucleic acid comprises RNA, it can also include regulatory sequences suitable to permit translation of the RNA. Thus, an RNA nucleic acid of the present invention preferably has at least one ribosome entry site, and preferably has a polyadenosine tail for stabilizing the RNA in the cellular environment.

Similarly, DNA nucleic acids of the present invention can have regulatory elements for promoting the transcription of sequence encoding the T-type calcium channel into an RNA such as that described above. For example, a DNA nucleic acid of the present invention can have a promoter and/or an enhancer sequence. While the nucleic acid can be any type of nucleic acid, the nucleic acid preferably comprises a cDNA. A cDNA nucleic acid is preferred over other nucleic acids to permit the nucleic acid to be readily cloned, sequenced, and expressed in a wide variety of cells.

The choice of promoter and/or an enhancer will largely depend on the milieu in which the nucleic acid is to be expressed. Thus, for expression in bacterial cells, the regulatory elements are bacterial promoters. Similarly, for expression in mammalian cells, the regulatory elements are able to effect expression in mammalian cells. While many such regulatory elements are known in the art, examples include prokaryotic promoters and viral promoters (e.g., retroviral ITRs, LTRs, immediate early viral promoters (IEp), such as herpesvirus IEp (e.g., ICP4-IEp and ICP0-IEp), cytomegalovirus (CMV) IEp, and other viral promoters, such as Rous Sarcoma Virus (RSV) promoters, and Murine Leukemia Virus (MLV) promoters). Other suitable promoters are eukaryotic promoters, such as enhancers (e.g., the rabbit  $\beta$ -globin regulatory elements), constitutively active promoters (e.g., the  $\beta$ -actin promoter, etc.), signal specific promoters (e.g., inducible promoters such as a promoter responsive to RU486, etc.), and tissue-specific promoters (e.g., those active in epidermal tissue, dermal tissue, tissue of the digestive organs (e.g., cells of the esophagus, stomach, intestines, colon, etc., or their related glands), smooth muscles, such as vascular smooth muscles, cardiac muscles, skeletal muscles, lung tissue, hepatocytes, lymphocytes, endothelial cells, sclerocytes, kidney cells, glandular cells (e.g., those in the thymus, ovaries, testicles, pancreas, adrenals, pituitary, etc.), tumor cells, cells in connective tissue, cells in the central nervous system (e.g., neurons, neuralgia, etc.), cells in the peripheral nervous system, and other cells of interest).

The isolated or substantially purified nucleic acid of the present invention encodes all or part of a T-type calcium channel  $\alpha$  subunit. As used herein, a "calcium channel" includes a protein structure for facilitating the flux of calcium ions across a biological membrane into which the calcium channel is inserted. As used herein, a "T-type channel" is a type of voltage-gated ion channel that facilitates the flux of ions

when the membrane potential of a biological membrane into which it is inserted experiences a slight depolarization. Thus, a T-type calcium channel can begin to gate from about -60 mV to about -30 mV (i.e., about -45 mV to about -35 mV) in about 10 mM  $Ba^{2+}$ . Additionally, T-type channels of the present invention exhibit a slow  
5 deactivation (tail current) following depolarization. Thus, a T-type calcium channel can exhibit a tail current that decays exponentially with a tau value from about 1 ms to about 10 ms (e.g., from about 4 ms to about 7 ms, such as about 6 ms) following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a  $Ba^{2+}$  concentration of from about 10 mM to about 40 mM. Another  
10 defining characteristic of T-type calcium channels is that they exhibit small single channel conductance. Thus, for example, a T-type channel exhibits a single channel conductance of from about 4 pS to about 12 pS (e.g., from about 6 pS to about 10 pS), and typically from about 7 pS to about 9 pS in a solution with a  $Ba^{2+}$  concentration of about 0.1 M.

15 The isolated or substantially purified nucleic acid of the present invention encodes all or part of any T-type calcium channel having at least one of the aforementioned electrophysiological properties when properly assembled within a cellular membrane. The general structure of calcium channels is summarized above and is otherwise known in the art. Thus, for example, the nucleic acid can encode one  
20 of the four functional domains mentioned above. As used herein, a domain of a T-type calcium channel is any protein structure able to associate with three other domains to form a tetrameric body functioning as a T-type calcium channel. While the native T-type calcium channel structure includes all four domains in a single polypeptide (indicated in Figures 1A-1E), a domain can exist as a polypeptide species  
25 separate from those containing the other domains. Such separate domains are able to associate within the plasma membrane to form a functional channel. Alternatively, where a plurality of domains are linked within a common polypeptide, the linkage can deviate substantially from the native linkage. Thus, for example, the domains can be linked by polypeptide sequences other than those sequences linking the domains in the  
30 native protein (e.g., non-native polyglutamate linkages). Indeed, the domains themselves can include non-native linkages between membrane-spanning elements within the domains. Aside from these modifications, the nucleic acid can encode a chimeric calcium channel domain (or an entire channel) comprising a portion of a T-type calcium channel and a portion derived from another calcium channel (or other  
35 channel) protein. For example, the chimera can include portions of domains from T-type channels responsible for low voltage gating and portions of domains from other calcium channels responsible for slow inactivation. Such a protein exhibiting T-type gating but longer inactivation kinetics would facilitate pharmacological research.

As mentioned, nucleic acids of the present invention can encode an entire T-type channel (i.e., a T-type channel protein comprising four functional domains). It has been discovered that at least three genes encoding T-type calcium channels exist in humans and rats (i.e.,  $\alpha 1G$  (or  $Ca_vT.1$ ),  $\alpha 1H$  (or  $Ca_vT.2$ ), and  $\alpha 1I$  (or  $Ca_vT.3$ )), and alternate splicing of these isoforms exist. Examples of the amino acid sequences of full-length T-type channels, and the sequences of suitable coding nucleic acids are set forth at SEQ ID NOs:1-8 ( $\alpha 1G$  sequences), SEQ IS NOs:9-10 ( $\alpha 1H$  sequences), and SEQ ID NOs: 11-12 ( $\alpha 1I$  sequences). However, the invention is not limited to these exemplary sequences. Indeed, as mentioned, an amino acid sequence of a T-type calcium channel can vary from those listed, and it is within the state of the art to change a nucleotide sequence encoding a T-type channel to introduce mutations into the protein. Indeed, for conducting electrophysiological assays, it may be desirable to introduce mutations into such a protein. For example, mutations comprising insertions or deletions can be introduced on either the amino- or carboxy-terminus of the protein, or such mutations can be intrasequence insertions or deletions. Where the electrophysiological properties of the calcium channel are to be conserved, such mutations preferably are in regions other than the membrane spanning domains. However, in some applications (e.g., to decrease inactivation kinetics), the changes can be within the membrane-spanning regions. Moreover, as mentioned above, the sequence can form a protein having only one functional domain of a T-type calcium channel. Additionally, the sequence can also form a chimeric protein or domain, such as those described above.

Aside from insertions and deletion mutations of native T-type calcium channel sequences, a T-type calcium channel can include substitutions of amino acid residues, e.g., for those indicated in SEQ ID NOs:1-12. Preferably, and especially where such a substitution is within a membrane spanning region, the substitution is conservative. Thus, within membrane spanning domains, positively-charged residues (H, K, and R) preferably are only substituted with positively-charged residues; negatively-charged residues (D and E) preferably are only substituted with negatively-charged residues; neutral polar residues (C, G, N, Q, S, T, and Y) preferably are only substituted with neutral polar residues; and neutral non-polar residues (A, F, I, L, M, P, V, and W) preferably are only substituted with neutral non-polar residues. Preferably, any amino-acid substitution within the membrane-spanning regions does not alter this conservation. Most preferably, any substitution, deletion, or insertion does not alter the IVS4 domain. In each of the exemplary T-type calcium channel  $\alpha$  subunit sequences, the putative IVS4 region comprises SEQ ID NO:13. Given the strong sequence conservation among families of voltage-gated ion channels, it is likely that this sequence or a derivative sequence, will be present in T-type channels. Thus, the

present invention provides any T-type calcium channel (or a nucleic acid encoding such a T-type calcium channel) comprising SEQ ID NO:13 or a sequence derived from SEQ ID NO:13 having conservative amino acid substitutions, as described above.

5           The nucleic acid of the present invention encoding all or a part of a T-type calcium channel can be isolated via any suitable method. For example, prior to the present invention, one of skill in the art could design a probe based on the sequence of known, non-T-type, calcium channels and use such probe to screen a genetic library. If such a screen were to identify a putative calcium channel, the researcher could then  
10 attempt to clone the entire nucleic acid to characterize it. Similarly, prior to the present invention, to isolate a nucleic acid encoding a T-type calcium channel, one of skill in the art could consult publicly available databases containing DNA sequences (e.g., Genbank) to locate nucleic or amino acid sequences representing a portion of a T-type calcium channel protein or nucleic acid. However, such databases contain no  
15 sequence for a full-length T-type calcium channel or identify any sequence as a T-type channel. Such methods assume that T-type calcium channels share sufficient sequence identity with known calcium channel nucleic acids to cross-hybridize, an assumption not supported by any published report. Moreover, prior to the present invention, no partial sequence in such databases was identified as corresponding to a  
20 T-type calcium channel. Thus, prior to the present invention, the presence of partial sequences in the public DNA databases could facilitate the isolation of T-type calcium channels only with the exercise of a considerable degree of speculation on the part of the researcher.

By providing several sequences pertaining to T-type calcium channels and a  
25 comparison presenting conserved regions and domains, the present invention greatly facilitates the isolation of other nucleic acids encoding T-type calcium channels (or derivatives thereof) with much less experimentation. Thus, while any of the methods discussed above can be employed to isolate other members of this genus, preferably, a nucleic acid encoding a T-type calcium channel is isolated by probing a genetic library  
30 using a probe that hybridizes to a DNA encoding a peptide sequence contained in (or similar to) a known T-type calcium channel (e.g., SEQ ID NOs:1-12). To facilitate the isolation of a T-type calcium channel, the present invention provides an isolated polynucleotide hybridizing to a portion of the nucleic acid of the present invention encoding a T-type calcium channel (or a portion thereof). Thus, for example, the  
35 present invention includes an isolated polynucleotide hybridizing to SEQ ID NO:1-12. The isolated polynucleotide can hybridize to all or any portion of the sequence encoding the T-type calcium channel.

To isolate such a polynucleotide, any portion of a sequence encoding a T-type calcium channel can be employed as a probe to screen a genetic library, and such screening can be accomplished by standard techniques known in the art. While the probe can hybridize to any portion of such a DNA, preferably the probe is designed to hybridize to a DNA encoding a polypeptide sequence that is highly conserved among T-type calcium channels but is less conserved between the genus of T-type calcium channels and other proteins. Such peptide sequences are readily apparent from the sequence comparison set forth in Figures 1A-1E. Generally, the specificity of hybridization in a genetic screen varies depending on the length of the probe and the stringency (e.g., temperature, salt and detergent concentration, etc.) of hybridization. Stringency of hybridization is broadly classified as "high," "moderate," or "low," and the parameters of these terms are well recognized in the art (see, e.g., Sambrook et al., "Molecular Cloning, a Laboratory Manual," Cold Spring Harbor Press, 1989). The isolated polynucleotide hybridizing to a portion of the nucleic acid encoding a T-type calcium channel can hybridize under any desired stringency conditions. However, for identifying other T-type channels, preferably, the hybridization occurs under moderate stringency, and most preferably under high stringency.

Of course, the isolated or substantially purified polynucleotide can itself be employed as a probe to screen a library as described to isolate a second nucleic acid. In such a screen, one of the polynucleotides will be complementary to a portion of the sequence encoding the T-type calcium channel, and the other isolated nucleic acid will be "sense." Preferably, one of the two isolated polynucleotides (the "sense" strand) itself encodes a T-type calcium channel, or at least one domain thereof. Such a sequence can be cloned to be operably linked to suitable regulatory elements, as described, to produce a T-type calcium channel. Thus, aside from using the nucleic acid of the present invention to produce a T-type calcium channel, the nucleic acids of the present invention are also useful for isolating other sequences encoding T-type calcium channels, or derivatives thereof.

However isolated, the isolated or substantially purified nucleic acid of the present invention is useful, in part, for producing all or a portion of a T-type calcium channel. Thus, the nucleic acid can be introduced into a suitable milieu for driving its expression. Because T-type channels are transmembrane proteins, preferably such a milieu is a living cell. However, it should be understood that the nucleic acid can also be expressed *in vitro* under conditions, such as those known in the art, suitable for *in vitro* transcription and translation. However produced, the present invention includes any protein, such as a recombinant protein or an isolated or substantially purified protein, including all or a portion of a T-type calcium channel or a protein derived from a T-type calcium channel.

For expression in a living cell, the nucleic acid must be introduced into the cell. As nucleic acids are generally introduced into cells as part of genetic vectors, the present invention provides a vector having a T-type calcium channel nucleic acid of the type described above. Any type of vector suitable for introducing the nucleic acid into a host cell is within the context of the present invention. Examples of such vectors include naked DNA and RNA vectors (such as oligonucleotides, plasmids, capped cRNA, etc.), viral vectors such as adeno-associated viral vectors (Berns et al., *Annals of the New York Academy of Sciences*, 772, 95-104 (1995)), adenoviral vectors (Bain et al., *Gene Therapy*, 1, S68 (1994)), herpesvirus vectors (Fink et al., *Ann. Rev. Neurosci.*, 19, 265-87 (1996)), packaged amplicons (Federoff et al., *Proc. Nat. Acad. Sci. USA*, 89, 1636-40 (1992)), papilloma virus vectors, picornavirus vectors, polyoma virus vectors, retroviral vectors, SV40 viral vectors, vaccinia virus vectors, and other vectors. Once a given type of vector is selected, its genome must be manipulated for use as a background vector, after which it must be engineered to incorporate exogenous polynucleotides. Such manipulations are known in the art.

The vectors of the present invention are useful for introducing a nucleic acid encoding all or a portion of a T-type calcium channel into a host cell. Thus, the present invention provides a cell into which the vector of the present invention has been introduced. The host cell can be any cell suitable for expressing the nucleic acid (e.g., bacteria, insect cells, mammalian cells, etc.). The host cell can thus be *in vitro* or *in vivo*. Preferably the cells do not exhibit native T-type calcium current. A preferred cell type is HEK-293 cells because they contain genetic elements that facilitate the expression of transgenes from a variety of expression vectors. For facilitating electrophysiological recordings, oocytes (e.g., *Xenopus* oocytes) are preferred, as they are large and readily handled.

The vector can be introduced into the cell in any manner suitable for the cell type and vector employed. In one embodiment, the vector can be used to prepare an RNA transcript *in vitro* (e.g., a capped cRNA) which is then introduced into the host cell by standard methods (such as injection). Such techniques are preferred when the host cells do not actively transcribe DNA (such as oocytes). In other embodiments, a DNA vector is introduced into the cell such that it is transcribed within the cell. For example, the vector can be introduced into the cell such that it forms an extrachromosomal segment of genetic material in the cell, as is the case with many types of viral vectors. Alternatively, the vector can introduce the nucleic acid into the chromosomal DNA of the host cell.

Preferably, a cell into which the nucleic acid is introduced is also able to express the nucleic acid to produce the  $\alpha$  subunit protein. The expression of the nucleic acid can be detected by probing the cell for the presence of T-type calcium

channel mRNA, such as via Northern hybridization analysis, in situ hybridization, etc. More preferably, however, the cell is able to express the nucleic acid to produce the protein including all or a portion of a T-type calcium channel. In such cells, expression of the nucleic acid is confirmed by detecting the protein, for example, by  
5 probing cellular extracts with an antibody recognizing the protein (e.g., on a Western blot, etc.).

In the membrane of the cell producing the protein, the expressed protein contributes to the formation of a functional calcium channel. Where the protein encodes an entire  $\alpha$  subunit, the full protein will possess some or all of the  
10 electrophysiological properties of T-type calcium channels described above. Where the protein encodes less than an entire channel  $\alpha$  subunit (e.g., a domain), the protein will aggregate with other constituent domains in the membrane to form a functional channel. Thus, the presence of the protein can be detected by assaying the cell for T-type calcium channel activity. Indeed, assaying for channel activity serves to  
15 determine whether a nucleic acid encoding a putative calcium channel, in fact, encodes a species of T-type channel (as opposed to a member of another genus of calcium channels). For example, when large cells (e.g., oocytes) are used as the host cells, the electrophysiological properties of the channel can be investigated. Thus, the membrane activity of whole cells expressing the nucleic acid can be measured  
20 directly, such as via patch clamp techniques using a voltage clamp electrode and a current electrode (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). Alternatively, the activity of single channels can be measured, such as with a standard depolarizing bath and pipette solutions (Lacerda et al., *Biophys. J.*, 66, 183-43 (1994)). However measured, the properties of cells into which the putative nucleic  
25 acid is introduced are compared to the channel conductance, voltage dependency, activation kinetics, inactivation kinetics, or tail current known for T-type channels and discussed above. A measure of current density (e.g., pA/pF) can also be used to assess the level of gene expression in the cells, normalizing for cellular volume.

While, in accordance with the present invention, an isolated cell into which the  
30 T-type calcium channel nucleic acid has been introduced (and preferably stably expressing the nucleic acid to produce the protein) can be prepared, preferably, such transfection protocols result in a population consisting essentially of such transfected cells. For standardizing the results of many experiments, it is even more desirable to employ an established cell line consisting essentially of such cells. Preferably, for use  
35 in high throughput assays, cell lines stably expressing a T-type calcium channel exhibit a current density of at least about 40 pA/pF (e.g., at least about 45 pA/pF), such as about 50 pA/pF or even 55 pA/pF or higher. Preferably, a cell line in accordance with the present invention is able to propagate the nucleic acid through



several passages (e.g., for at least 10 passages), and, preferably, the nucleic acid is stably integrated into the chromosomes of such cells. Thus, the cell line can propagate the nucleic acid for at least 20 passages, and more preferably significantly more than 20 passages (e.g., at least about 25 passages, or even more).

5           Regardless of the cell system, the ability to express a T-type calcium channel nucleic acid within host cells to produce an active channel permits the channel to be further studied. In this regard, the present invention provides a method of identifying a drug which affects T-type calcium channels. The method involves first expressing a T-type calcium channel in a cell to produce an active channel, as herein described.

10       The cell expressing the channel is then exposed to a solution containing a putative drug for interfering with the channel. Thereafter, the presence or absence of calcium flux in response to a change in membrane potential is assayed. Any such assay can be employed within the context of the present invention, (e.g., using labile dyes, radioisotopes (e.g.,  $^{45}\text{Ca}$ ), recording electrophysiological changes in the membrane,

15       etc.). A quick method of assaying for calcium flux is first to introduce a calcium-sensitive labile dye into the cells. For example, the dye can be one such as those that fluoresce or change color in the presence of calcium, many of which are known to those of skill in the art (e.g., Indo-1). Thereafter, the cells are exposed to a depolarizing solution containing high (e.g., about 50 mM) potassium concentration

20       and a drug, and the reaction of the labile dye is compared to control cells. Using a labile dye affords the ability to assay many putative drugs quickly in a high throughput assay for putative drugs affecting T-type channels. For example, the initial screening can be carried out in 96 well plates. Moreover, dose-response data can be readily generated by exposing the cells to several concentrations of the same putative

25       drug.

          Once a putative drug is detected, its effect on the electrophysiology of the cell (e.g., single channel conductance, voltage dependency, activation kinetics, inactivation kinetics, and tail current of the cells) can be investigated in detail. Generally, the effect of the putative drug on T-type calcium currents is assessed by

30       measuring the various electrophysiological parameters in the presence of various concentrations of the drugs and comparing the data to untreated (or sham-treated) control cells. Cells preferably are maintained in a continuous perfusion chamber during such experiments to facilitate changing solutions. The inventive method of identifying a drug which affects T-type calcium channels can employ any nucleic acid

35       encoding a T-type calcium channel (or derivative thereof), such as those nucleic acids described herein. In fact, as several isoforms of T-type channel exist, the assay method can be repeated using nucleic acids encoding different isoforms to identify

drugs that preferentially target a given isoform, or drugs which affect more than one isoform of T-type calcium channels.

Aside from affording an *in vitro* assay for detecting potential therapeutic or investigative drugs targeting T-type calcium channels, the method of expressing the T-type calcium channel nucleic acid can also be used *in vivo*. For example, as mentioned, several neurological and muscular diseases or disorders have implicated mutations affecting native nucleic acids encoding T-type calcium channels. The present invention, thus, provides a method of treating a disease or disorder associated with a deficiency in a native T-type calcium channel nucleic acid. The method involves introducing a vector having the T-type calcium channel nucleic acid into cells of a host in which native expression of the nucleic acid is deficient. Thus, for example, for treating cardiomyopathy associated with deficiencies in T-type calcium channels, the vector is introduced into myocardial cells. Similarly, for treating forms of epilepsy associated with deficiencies in T-type calcium channels, the vector is introduced into neurons (e.g., thalamic neurons). Within the target cells, the nucleic acid within the vector is expressed to produce active T-type calcium channel. By similar methods, an nucleic acid having a sequence antisense to a sequence encoding a T-type calcium channel (or a portion thereof) can be expressed within a cell. The presence of an antisense sequence can down-regulate the expression of native T-type calcium channel genes by hybridizing to T-type channel mRNA within the cell. Thus, the present invention is useful to treating disorders associated with over-expression of T-type calcium channels.

T-type channel proteins (such as whole T-type calcium channels, domains of such channels, chimeras including portions of T-type calcium channels, etc.) can be employed to generate antibodies (e.g., immunoglobulins) to T-type calcium channels. Thus, the present invention provides an isolated and substantially purified antibody molecule recognizing an epitope on a T-type calcium channel. Such antibodies can be monoclonal antibodies or polyclonal antisera. Antibodies recognizing T-type calcium channels can be used to purify the channels from cell extracts or other solutions by standard methodologies (e.g., immunoprecipitation). Moreover, depending on the location of the epitopes for the antibodies on the T-type calcium channel, the antibodies can be used to affect the channel proteins present on the surface of cells. Thus, antibodies directed to T-type calcium channels are potential reagents for studying the channels as well as for therapy.

Such antibodies can be produced by any suitable method, many of which are well known in the art. Thus, for example, the antibodies can comprise polyclonal antisera obtained from inoculated animals. Alternatively, the antibody molecules can be monoclonal antibodies obtained from a cell line (e.g., a hybridoma cell line). Thus,

the present invention provides a cell which produces such antibodies. Such a cell can be *in vitro* or *in vivo*; however, where the cell is *in vitro*, preferably it is within an established cell line consisting essentially of such cells.

Several examples are presented below to illustrate the invention. Taken  
5 together, the examples demonstrate the cloning of twelve novel proteins and their characterization as T-type calcium channel  $\alpha$  subunits. These examples are included here for purely illustrative purposes; as such, they are not to be construed so as to limit the scope of any aspect of the invention.

Many procedures employed in the following examples are techniques routinely  
10 performed by one of ordinary skill in the art (see generally Sambrook et al., *Molecular Cloning. A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY (1989)) and are not discussed in detail. However, some reagents and methods deserve specific description. Thus, for example, *in vitro* translation and expression were conducted as described previously (Schneider et al., *Receptors and Channels*, 2,  
15 255-70 (1995)). *Xenopus laevis* oocytes were prepared as described previously (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). To express proteins, 10 or 30 ng of capped cRNA was injected into the oocytes in a volume of 50 nl. For single channel recording, oocytes were injected with 100 ng capped cRNA and incubated for one week prior to assay.

20 Cells were voltage clamped using a two-microelectrode voltage clamp amplifier as described (Bernal et al., *J. Pharmacol. Exp. Ther.*, 282, 172-80 (1997)). The standard bath solution contained the following: 40 mM Ba(OH)<sub>2</sub>, 50 mM NaOH, 1 mM KOH, 0.1 mM EDTA, and 5 mM HEPES, adjusted to pH 7.4 with methanesulfonate. The osmolality of the 2 mM Ba<sup>2+</sup> and 10 mM Ba<sup>2+</sup> solutions was  
25 balanced by increasing the NaOH concentration as described (Lory et al., *J. Physiol.*, (London), 429, 95-112 (1990)). Voltage and current electrodes (1.5-1.8 M tip resistance) were filled with 3 M KCl. Except as noted, data were acquired at 4 kHz using the pCLAMP system, and filtered at 1 kHz. Data were analyzed using pCLAMP software. Boltzman fits and linear regression were calculated using Prism.

### 30 EXAMPLE 1

This example demonstrates the cloning and characterization of putative T-type calcium channels.

A search of the Genbank library was conducted to identify clones identified as  
35 having some degree of homology to known calcium channel sequences. The search identified an expressed sequence tagged (EST) partial sequence in a human brain clone (H06096), which was used as a probe to screen a  $\lambda$ gt10 cDNA library prepared

from rat brain. Successive screening of the cDNA library identified five overlapping clones which were aligned to construct an entire cDNA sequence, termed  $\alpha 1G$ .

5 The  $\alpha 1G$  cDNA was cloned into the pSP72<sup>TM</sup> vector and sequenced by standard computer-assisted sequencing. Using the  $\alpha 1G$  cDNA, the amino acid sequence of the  $\alpha 1G$  protein was deduced and compared to the sequences of other known calcium channel  $\alpha$  subunits. By similar methods, homologous human (H19230 and R19524) and mouse (AA286626) EST clones were also identified and partially sequenced, and alternately spliced variants were identified. The deduced cDNA and amino acid sequences for eight full-length  $\alpha 1G$  T-type channels are set forth, respectively, as SEQ ID NOs:1-8.

10 A second T-type calcium channel, termed  $\alpha 1H$ , was isolated by screening a human heart cDNA library with a fragment of the  $\alpha 1G$  sequence. An alternately spliced isoform was also identified. The full-length cDNA and amino acid sequences for these  $\alpha 1H$  T-type channels are set forth, respectively, as SEQ ID NOs:9 and 10.

15 A third T-type calcium channel, termed  $\alpha 1I$ , was isolated by screening a rat brain cDNA library at low stringency using a fragment of the rat  $\alpha 1G$  gene. Fifty plaques were identified, many of which were not detected in a second screening. A third screening with a fragment from  $\alpha 1H$  identified two clones. Subsequent screening, and the use of the GenBank database, led to the identification of the full length rat and human cDNA and amino acid sequences, set forth at SEQ ID NOs: 11 and 12, respectively.

20 The  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  amino acid sequences were compared to each other and a known calcium channel ( $\alpha 1E$ ) to investigate the conservation of protein structure and function. The comparison indicates that the  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  amino acid sequences within the putative membrane-spanning domains are about 90 % identical to each other, while the  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  sequences are only roughly 40 % identical to the  $\alpha 1E$  clone.

25 Figures 1A-1E indicate this conservation between the proteins. The conservation of charged residues, particularly in the S4 domains, is consistent with the role of the  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  proteins as ion channels. However, two of the glutamates associated with ion specificity in other calcium channels have been replaced with aspartate, suggesting altered ion selectivity. Strikingly,  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  display only low homology to sequences linking the membrane-spanning regions within each domain, and even less homology between the intracellular loops linking domains. Notably, neither  $\alpha 1G$ ,  $\alpha 1H$ , nor  $\alpha 1I$  possesses sequences known to bind  $\beta$  subunits or  $Ca^{2+}$  ions.

## EXAMPLE 2

This example demonstrates the production of cell lines stably expressing the cloned  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  proteins.

HEK-293 cells were transfected with either the rat  $\alpha 1G$  cDNA (SEQ ID NO:1), the human  $\alpha 1H$  cDNA (SEQ ID NO:9), or the rat  $\alpha 1I$  cDNA (SEQ ID NO:11). As a control, cells were also transfected with human  $\alpha 1E$  plus human  $\beta 3$  (Schneider et al., *Receptors Channels*, 2, 255-70 (1994); Murakami et al., *Eur. J. Biochem.*, 236, 138-43 (1996)). The DNA constructs included a neomycin resistance gene conferring resistance to G418. The cells were cultured under standard conditions using medium containing G418 to select for stable transformants.

Surviving clones were expanded and assayed for electrophysiological activity to determine the presence of channels within the membrane. Whole-cell currents were recorded from ruptured patches using an Axopatch 200A amplifier, Digidata 1200 A/D converter, and pCLAMP 6.0 software. Data were digitized at 2 kHz and filtered at 1 kHz or off-line. All experiments were performed at room temperature. Pipettes were made out of TW-150-6 capillary tubing (World Precision Instruments, Inc., Sarasota, FL), using a Model P-97 Flaming-Brown pipette puller (Sutter Instrument Co., Novato, CA). The internal pipette solution contained the following: 55 mM CsCl, 75 mM CsSO<sub>4</sub>, 10 mM MgCl<sub>2</sub>, 0.1 mM EGTA, 10 mM HEPES, pH adjusted to 7.2 with CsOH. The external Tyrodes solution was the following: 140 mM NaCl, 6 mM KCl, 2 mM CaCl<sub>2</sub>, 10 mM glucose, 5 mM HEPES, pH 7.4. The recording solution contained the following: 10 mM BaCl<sub>2</sub> solution (or 2 mM CaCl<sub>2</sub>), 140 mM tetraethylammonium (TEA) chloride, 5 mM CsCl, 1 mM MgCl<sub>2</sub>, 5 mM glucose, and 10 mM HEPES, pH adjusted to 7.4 with TEA-OH. Under these solution conditions the pipette resistance was typically 1.5-2.5 M $\Omega$ . Cell capacitance was measured by integrating the charging current during a 10 mV hyperpolarizing pulse (holding potential -80 mV).

Using these recording techniques, values for pA/pF were obtained for each cell line, which is a measure of current density normalizing for cell size. One clone (#N2) expressed the rat  $\alpha 1G$  protein and has a current density of 42 pA/pF. Another clone (#13), expressed the human  $\alpha 1H$  protein and exhibited a current density of 53 pA/pF. Three clones (#11, #19, and #25) expressed the rat  $\alpha 1I$  protein and exhibited current densities of 40 pA/pF, 45 pA/pF, and 55 pA/pF, respectively.

## EXAMPLE 3

This example demonstrates that the cloned putative T-type calcium channels exhibit T-type current-voltage relationships.

Current traces were elicited by depolarizing voltage clamp pulses of the membranes of cells. The  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  proteins were produced in *Xenopus laevis* oocytes by linearizing the DNA vectors containing the coding sequences, and transcribing the coding sequences *in vitro* by standard methods. Oocytes were then  
5 injected with the capped RNA.

Figures 2A-2E depict data obtained from these experiments using cells injected with  $\alpha 1G$  (Figure 2A),  $\alpha 1H$  (Figure 2B), and  $\alpha 1I$  (Figure 2C) and  $\alpha 1E$  (Figure 2D). These data indicate that cells expressing  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  exhibit T-type calcium current, while oocytes expressing  $\alpha 1E$  as well as uninjected oocytes (Figure 6A) do  
10 not.

Current voltage curves were developed using cells injected with  $\alpha 1G$ ,  $\alpha 1H$ ,  $\alpha 1I$ , and  $\alpha 1E$ . Figures 3A depicts such data generated in a 10 mM  $Ba^{2+}$  test solution. These data were transformed into conductance and fit with a Boltzman equation to determine the midpoint of activation ( $V_{0.5}$ ). Gating potentials for  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$   
15 ( $-38 \pm 1$  mV  $n=8$ ,  $-44$  mV  $\pm 1$  mV,  $n=10$ , and  $-31$  mV  $\pm 1$  mV,  $n=6$ , respectively) were in accordance with the gating potential measured for the HEK-293 cells ( $-41 \pm 1$  mV,  $n=10$ ), while  $\alpha 1E$  required significantly more positive potentials to open ( $-2.6$  mV  $\pm .4$  mV,  $n=3$ ).

To compare the characteristics with published values (Huguenard, *Ann. Rev. Physiol.*, 58, 329-48 (1996)), the  $\alpha 1G$  current was recorded at varying concentrations of  $Ba^{2+}$ . As indicated in Figure 3B, in solutions containing 2 mM  $Ba^{2+}$ ,  $V_{0.5}$  was  $-46.5$  mV, and the slope factor ( $k$ ) was 6.6 ( $n=7$ ). However, when the  $Ba^{2+}$  concentration was 40 mM,  $V_{0.5}$  was recorded at  $-21$  mV, presumably due to the results of barium on surface charge screening (see, e.g., Wilson et al., *J. Membrane Biol.*, 72, 117-30  
20 (1983)). Similar values were recorded for  $\alpha 1H$  and  $\alpha 1I$ .

These results indicate that  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  are low-voltage activated calcium channels (i.e., from about  $-60$  mV to about  $-30$  mV in 10 mM  $Ba^{2+}$ ).

#### EXAMPLE 4

30 This example demonstrates that the cloned putative T-type calcium channels exhibit T-type tail current.

Tail current was measured at  $-90$  mV after first opening the channels with a voltage step to  $-10$  mV. The voltage-dependence of tail current in cells expressing  $\alpha 1G$  (oocytes)  $\alpha 1H$  (HEK 293 cells), and  $\alpha 1I$  (HEK 293 cells) was measured at  
35 varying test potentials. As a control, tail current was also measured from a high voltage activated channel  $\alpha 1E$ , which Raw data from recordings data were fit with a single exponential and plotted as a function of depolarization potential (Figure 4).

These results demonstrate that the tail currents for the cloned  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  calcium channels are voltage-dependent, consistent with known T-type calcium tail currents. Additionally, these data demonstrate that the tail current for each of the cloned channels is between about 1 ms and about 10 ms following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a barium concentration of from about 10 mM to about 40 mM.

#### EXAMPLE 5

This example demonstrates that the cloned putative T-type calcium channels exhibit T-type single channel conductance.

Measurement of single channel conductance is complicated by the low probability of channel opening at negative potentials when the driving force is large. Thus, single channel conductance was measured similarly for measurements of tail currents to enhance channel opening at negative potentials. Single channels were measured with standard depolarizing bath and pipette (115 mM  $BaCl_2$ , 1 mM EGTA, and 10 mM HEPES, pH 7.4) solutions (Lacerda et al., *Biophys. J.*, 66, 1833-43 (1994)). Data were analyzed with TRANSIT (VanDongan, *Biophys. J.*, 70, 1303-15 (1996)). Single channel amplitudes were measured by averaging the values obtained from Gaussian fits to all-points histograms of traces with openings, selected openings, or amplitude histograms of idealized openings. It has been reported that some oocytes contain a native 9 pS channel. These endogenous channels can be distinguished by their 2-fold larger current amplitudes at the potentials tested (e.g., -20 mV,  $i = 0.8$  for endogenous channels as opposed to 0.4 pA for  $\alpha 1G$ ). However, such endogenous channels were not detected either at the whole cell or single channel level in the oocytes tested.

Current through the main open state of each open channel was measured at each potential and plotted against each test potential. Single channel currents for several patches were then averaged and plotted as a function of test potential, wherein the slope of the plot indicated the single channel conductance. The average slope conductance of the  $\alpha 1G$  channel was measured at  $7.5 \pm 1.5$  pS, which corresponds with the reported values for T-type calcium channels (Huganard, *Ann. Rev. Physiol.*, 58, 329-48 (1996)). Similar results were also obtained with both  $\alpha 1H$  ( $10.8 \pm 1.4$  pS). Data collected from recordings of the  $\alpha 1I$  channels indicate that they open to two distinct amplitudes. The conductance for the small amplitude  $\alpha 1I$  openings was measured at  $3.9 \pm 0.5$  pS, while that for the large  $\alpha 1I$  openings was measured at  $11.4 \pm 0.5$  pS).

These results indicate that the cloned  $\alpha 1G$ ,  $\alpha 1H$ , and  $\alpha 1I$  proteins exhibit T-type single-channel conductance (e.g., from about 4 to about 12 pS).

## EXAMPLE 6

This example demonstrates that a cloned T-type calcium channel can be used for identifying a drug which affects T-type calcium channels.

5 HEK-293 cells were subjected to treatment as indicated above in Example 3, except that an experimental group of cells were exposed to a solution containing 1  $\mu$ M mibefradil, a known inhibitor of T-type calcium current. As depicted in Figure 5A, the presence of mibefradil almost completely abolished T-type current in cells  
10 expressing  $\alpha$ 1G. Cells expressing either  $\alpha$ 1G or  $\alpha$ 1H were similarly treated using various concentrations of mibefradil to determine a dose-response relationship. These results, depicted in Figure 5B, demonstrate that about 50% inhibition was achieved at a mibefradil concentration of 1  $\mu$ M.

15 All of the references cited herein, including patents, patent applications, and publications, are hereby incorporated in their entireties by reference.

While this invention has been described with an emphasis upon preferred  
embodiments, it will be obvious to those of ordinary skill in the art that variations of  
the preferred embodiments may be used and that it is intended that the invention may  
be practiced otherwise than as specifically described herein. Accordingly, this  
20 invention includes all modifications encompassed within the spirit and scope of the  
invention as defined by the following claims.



What is claimed is:

1. A isolated or substantially purified nucleic acid encoding a protein comprising at least one domain of a T-type calcium channel  $\alpha$  subunit.

2. The nucleic acid of claim 1, wherein said protein comprises an entire T-type calcium channel  $\alpha$  subunit.

3. The nucleic acid of claim 2, wherein said protein comprises SEQ ID NO:13.

4. The nucleic acid of any of claims 1-3, wherein said calcium channel begins to gate from about -60 mV to about -30 mV in 2 mM  $\text{Ba}^{2+}$ .

5. The nucleic acid of any of claims 1-4, wherein said calcium channel exhibits a tail current of from about 1 ms to about 10 ms following repolarization to a membrane potential from about -80 mV to about -60 mV in a solution with a barium concentration of from about 10 mM to about 40 mM.

6. The nucleic acid of any of claims 1-5, wherein said calcium channel exhibits a single channel conductance of from about 4 pS to about 11 pS in a solution with a barium ion concentration of about 100 mM.

7. An isolated or substantially purified nucleic acid hybridizing to the nucleic acid of any of claims 1-6.

8. An isolated or substantially purified nucleic acid hybridizing to the nucleic acid of claim 7.

9. The nucleic acid of claim 8 comprising a sequence encoding at least one domain of a T-type calcium channel  $\alpha$  subunit.

10. A vector comprising the nucleic acid of any of claims 1-9.

11. A cell into which the vector of claim 10 has been introduced.

12. The cell of claim 11, which expresses said nucleic acid to produce said protein.

13. The cell of claim 11 or 12, which stably expresses said nucleic acid to produce said protein.

14. A population of cells consisting essentially of cells according to any of claims 11-13.

15. An established cell line consisting essentially of cells according to any of claims 11-13.

16. A method of identifying a drug which affects T-type calcium channels, said method comprising expressing a T-type calcium channel in a cell, exposing said cell to a putative drug, and measuring the calcium flux through the membrane of said cell in response to a change in membrane potential.

17. The method of claim 16, wherein said calcium flux is assayed by using a calcium-sensitive labile dye within said cell.

18. The method of claim 16, wherein said calcium flux is assayed by measuring the electrophysiological properties of said cell.

5 19. The method of claim 16, wherein said calcium channel comprises SEQ ID NO:13.

20. An isolated or substantially purified immunoglobulin recognizing an epitope on a T-type calcium channel protein.

21. A cell *in vitro* which produces the immunoglobulin of claim 20.

10 22. An established cell line consisting essentially of cells according to claim 21.

hCavT1a MDEEDGAGAEESGQPR-----SFMRLNDLSGAGRPGPSAEKDPGSADSEAEGLPYPALAPVVFYLSQDSRRPRSWCLRTVCNPW  
 rCavT1a MDEEDGAGAEESGQPR-----SFTQNDLSGAGRQCPGSTEKDPGSADSEAEGLPYPALAPVVFYLSQDSRRPRSWCLRTVCNPW  
 hCavT2a MTEGARAADVRVPLGRRFWPCGCGVGPCEPRGAGTRGGGFFGVSPSEPAARCAELGADEEQRVYPYALAAATVFFCLGQTRPRSWCLRLVVCNPW  
 hCavT3 MAESASPPSSAAA-----PAAEPGVTEQPGPRSPSPSGLEELDGDADPHVPHDLAPIAFFCLRQTTSPRNWCIRKAVVCNPW  
 rCavT3 MADSNLPPSSAAAP-----APEPG--ITEQPGPRSPSPSGLEELDGDADPHVPHDLAPVAFVAFCLRQTTSPRNWCIRKAVVCNPW

IS1  
 hCavT1a FERISMLVILLNCVTILGMRPCEDTACDSQRCRILQAFDDFIEAFFAVEMVVKMVALGIFGKKCYLGD<sup>IS2</sup>TWNRDFFI<sup>IS3</sup>VIAGMLEYSLDLQNVSESAVRTV  
 rCavT1a FERVSMVLVILLNCVTILGMRPCEDTACDSQRCRILQAFDDFIEAFFAVEMVVKMVALGIFGKKCYLGD<sup>IS2</sup>TWNRDFFI<sup>IS3</sup>VIAGMLEYSLDLQNVSESAVRTV  
 hCavT2a FEHVSMLVIMLNCVTILGMRPCEDVECGSERCNILEAFDAFIEAFFAVEMVVKMVALGIFGKKCYLGD<sup>IS2</sup>TWNRDFFI<sup>IS3</sup>VIAGMLEYSLDLQNVSESAVRTV  
 hCavT3 FECVSMVLVILLNCVTILGMYQPCDDMDCLSDRCKIMQVDDFIEIFFAMEMVLKMMVALGIFGKKCYLGD<sup>IS2</sup>TWNRDFFI<sup>IS3</sup>VIAGMLEYSLDLQNVSESAVRTV  
 rCavT3 FECVSMVLVILLNCVTILGMYQPCDDMECLSDRCKILQVDDFIEIFFAMEMVLKMMVALGIFGKKCYLGD<sup>IS2</sup>TWNRDFFI<sup>IS3</sup>VIAGMLEYSLDLQNVSESAVRTV

IS4  
 hCavT1a RVLRLRAINRVPSMRILVTLILLDTPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRNRCFLPENFSLPLSVD-LERYYQTENEDESPFICSQPRENGMRS  
 rCavT1a RVLRLRAINRVPSMRILVTLILLDTPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRNRCFLPENFSLPLSVD-LERYYQTENEDESPFICSQPRENGMRS  
 hCavT2a RVLRLRAINRVPSMRILVTLILLDTPMLGNVLLLCFFVFFIFGIVGVQLWAGLLRNRCFLDFAVRNNLTFLRPYYQTEEGEENPFICSSRRDNGMQK  
 hCavT3 RVLRLKAINRVPSMRILVNLILLDTPMLGNVLLLCFFVFFIFGIIIGVQLWAGLLRNRCFLEENFTIQGDVA-LPPYYQPEEDEMPPFICSLSGDNGIMG  
 rCavT3 RVLRLKAINRVPSMRILVNLILLDTPMLGNVLLLCFFVFFIFGIIIGVQLWAGLLRNRCFLEENFTIQGDVA-LPPYYQPEEDEMPPFICSLTGDNGIMG

IP LOOP  
 hCavT1a CRSVPTLRGDG-----GGGPPCGLDYEAYNSSNTTCVNNQYYTNCSSAGEHNPFKGA<sup>IS5</sup>INFNIGYAWIAIFQVITLEGWVDIMYFVMDAHSFYNFIFYFI  
 rCavT1a CRSVPTLRGEG-----GGGPPCSLDYETYNSSNTTCVNNQYYTNCSSAGEHNPFKGA<sup>IS5</sup>INFNIGYAWIAIFQVITLEGWVDIMYFVMDAHSFYNFIFYFI  
 hCavT2a CSHIPGRDVRMPCTLGWEA-YTQPAEGVGAARNACINWNQYYNVCRSNPHGAINFNTCYAWIAIFQVITLEGWVDIMYFVMDAHSFYNFIFYFI  
 hCavT3 CHEIPPLKEQGRECCLSKDDVYDFGAGRQDLNASGLCVNNRYYNVCRVTCGSANPHKGA<sup>IS5</sup>INFNIGYAWIVIFQVITLEGWVEIMYFVMDAHSFYNFIFYFI  
 rCavT3 CHEIPPLKEQGRECCLSKDDVYDFGAGRQDLNASGLCVNNRYYNVCRVTCGSANPHKGA<sup>IS5</sup>INFNIGYAWIVIFQVITLEGWVEIMYFVMDAHSFYNFIFYFI

IS6  
 hCavT1a LLIIVGSFFEMINCLVVIATQFSETKQRESQMLREQVRVRLSNASTLASFSEPGSCYEEILLKYLVIYLKKAARRLAQVSRAAGVRVGLLSSPAPLGGQET  
 rCavT1a LLIIVGSFFEMINCLVVIATQFSETKQRESQMLREQVRVRLSNASTLASFSEPGSCYEEILLKYLVIYLKKAARRLAQVSRAIGVRAGLLSSPVARSQEP  
 hCavT2a LLIIVGSFFEMINCLVVIATQFSETKQRESQMLREQVRARHLNSDSTLASFSEPGSCYEEILLKYLVIYLKKAARRLAQVSRAIGVRAGLLSSPVARSQEP  
 hCavT3 LLIIVGSFFEMINCLVVIATQFSETKQREHRLMLEQRQRYLSS-STVASYAEPGDCYEEIFQYVCHILKAKRRALGLYQALQRRQ-----  
 rCavT3 LLIIVGSFFEMINCLVVIATQFSETKQREHRLMLEQRQRYLSS-STVASYAEPGDCYEEIFQYVCHILKAKRRALGLYQALQRRQ-----

Fig. 1A

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hCavT1a QPSSSCSRHRLSVHHLVHHHHHHHHYHLGNGCTLRAPRASPEIQDRDANGSRRLMLPPPSTPALSGAPPGA-----ESVHSFYHADCHLEPVRC
rCavT1a QPSGSCSTRHRLSVHHLVHHHHHHHHYHLGNGCTLRVPRASPEIQDRDANGSRRLMLPPPSTPTSGGPPRGA-----ESVHSFYHADCHLEPVRC
hCavT2a GHRQRAGRHTASVHHLVHHHHHHHHHHYHFSHGSPRRPGPEPGACDTRLVRAGAPPPSPSPGRGPPDAESVHSFYHADCHIEGPQERARVGTCTRSHCRC
hCavT3 -----
rCavT3 -----

hCavT1a QAPPPRSPSEASGRITVGSGKVYPTVHTSPPPETLKEKALVEVAASSGPTLTSLN-IPPGPYSSMHKLELTQSTGACQSSCKISSPCLKADSGACGPDSC
rCavT1a QAPPPRCPSEASGRITVGSGKVYPTVHTSPPPETLKD KALVEVAPSPGPTLTSEN-IPPGPFSSMHKLELTQSTGACHSSCKISSPCSKADSGACGPDSC
hCavT2a QPQAGRAGHHHELPHDPALRGQRQRQHQPRTQGEVGRWTARHRGHGPLSLNSPDYKIPHVAGSHGLGQAPGHLGSLVPCPLPSPAGTLTCELKSC
hCavT3 -----
rCavT3 -----

hCavT1a PYCARA-GAGEVELADREMPDSDSEAVYFTQDAQHSLRDPHS-----RR-QRSLGPDAPSSVLAFWRLICDTRFKIVDSKYFGRGIM
rCavT1a PYCART-GAGEPESADHVPDSDSEAVYFTQDAQHSLRDPHS-----RRQRSLSGPDAPSSVLAFWRLICDTRFKIVDSKYFGRGIM
hCavT2a PYCTRALEDPEGELSGSESGSDGRGVYFTQDVRHGRWDPTPRATDTPGPGSPORRAQRAAPGEPGMGRMLWVTFSGKLRRIVDSKYFGRGIM
hCavT3 PCQHEGRRPSGLGSTD SGQEGS-----GSGSSAGGEDEADGDGARSSEDDGASSELGKEEEEEQADGAVLWCGDVWRETRAKLRGIVDSKYFNRGIM
rCavT3 PHCQHEAGRRPSGLGSTD SGQEGS-----GSGCSA--EAEANGDLQSSDDGVSSDLGKEEQE---DGAARLWCGDVWRETRAKLRGIVDSKYFNRGIM

IIS1
hCavT1a IAILVNTLSMGIEYHEQPEELTNALIEISNIVFTSLFALEMLLKLIVYGPFGYIKNPYNIFDGVIVVISVWEIVGQGGGLSVLRTFRLMRVLKLVRELP
rCavT1a IAILVNTLSMGIEYHEQPEELTNALIEISNIVFTSLFALEMLLKLIVYGPFGYIKNPYNIFDGVIVVISVWEIVGQGGGLSVLRTFRLMRVLKLVRELP
hCavT2a MAILVNTLSMGIEYHEQPEELTNALIEISNIVFTSMFALEMLLKLACGGLGYIRNPYNIFDGIIVVISVWEIVGQADGGLSVLRTFRLMRVLKLVRELP
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```

Fig. 1B

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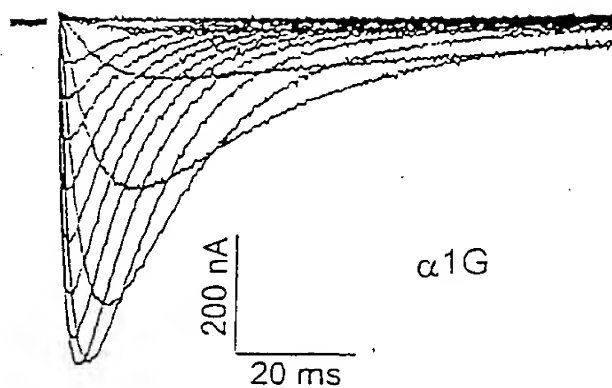
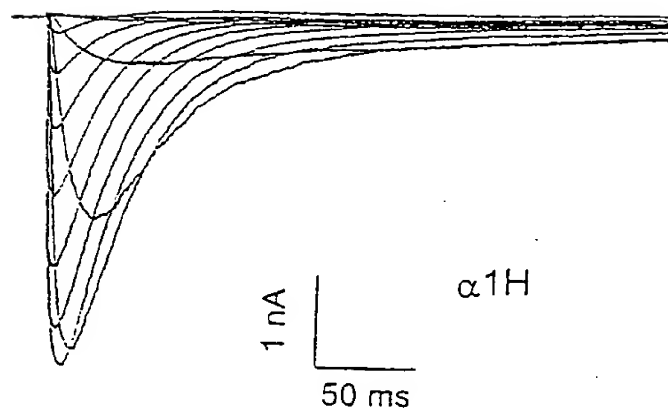
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Fig. 1C

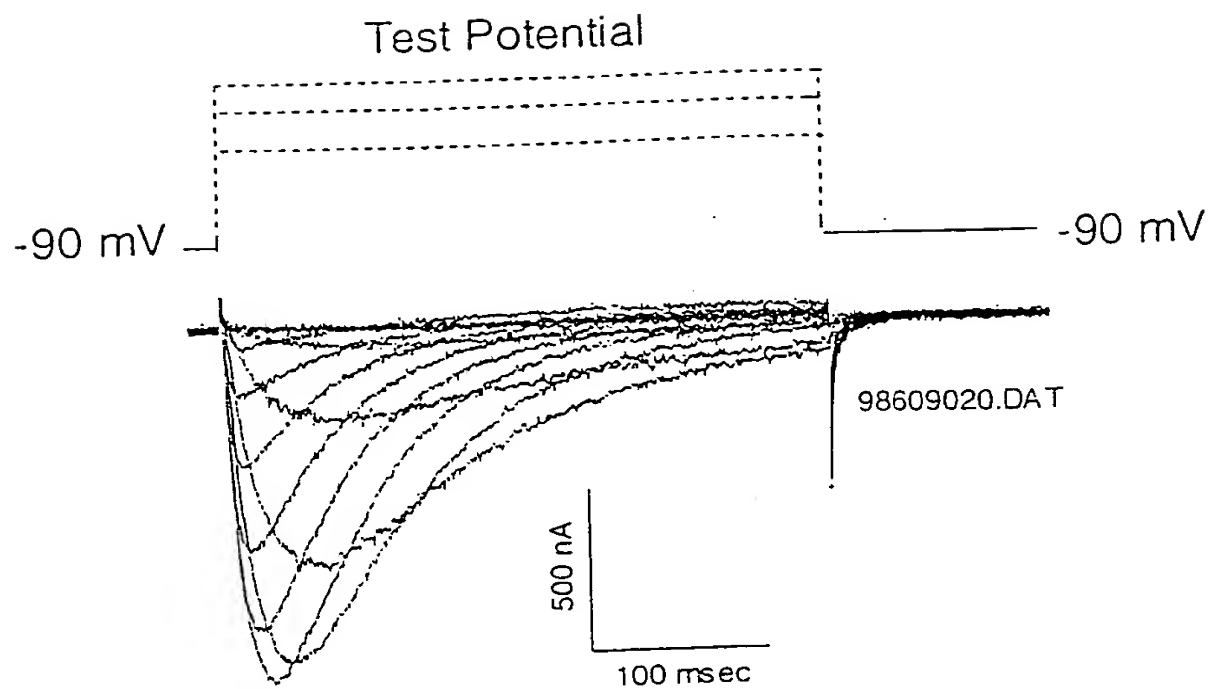
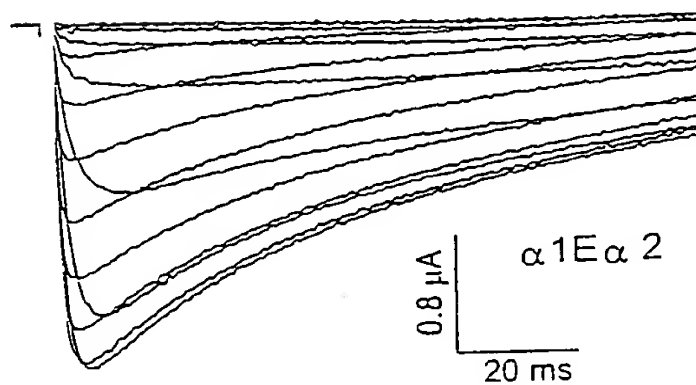


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Fig. 1E

**Figure 2A****Figure 2B**



**Figure 2C****Figure 2D**

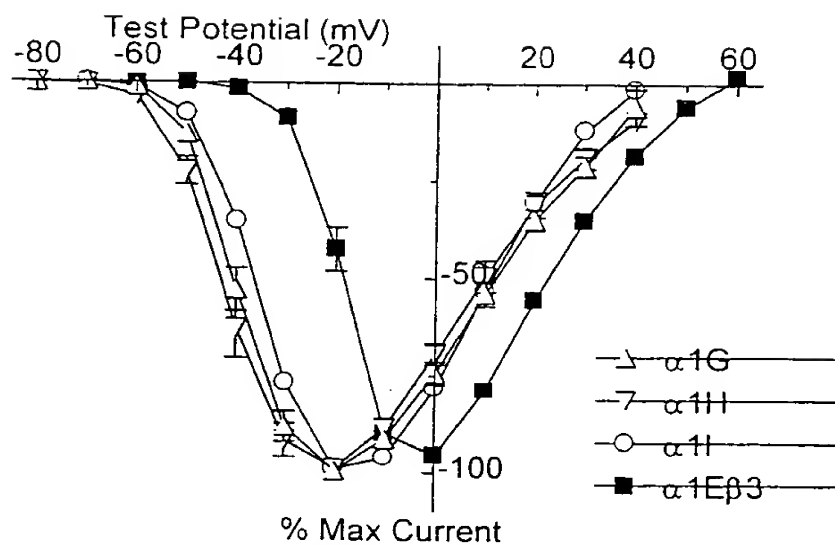


Figure 3A

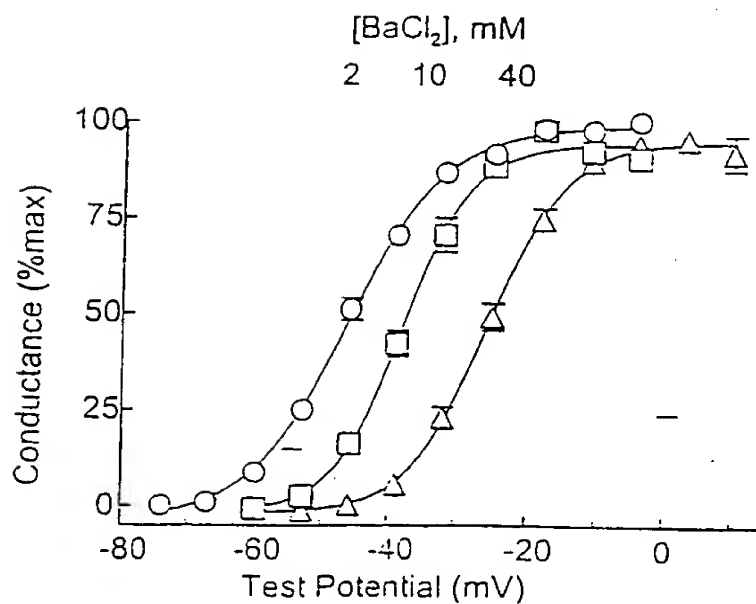
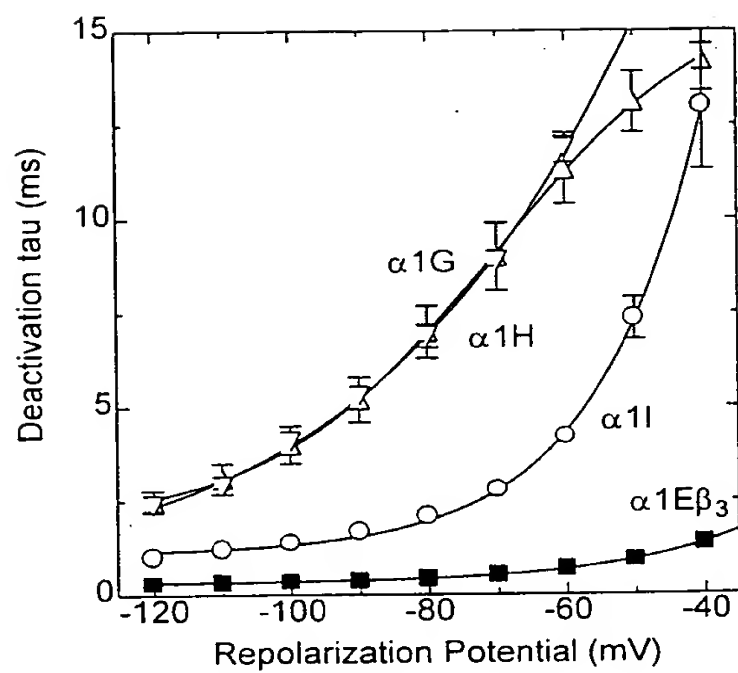


Figure 3B

**Figure 4**

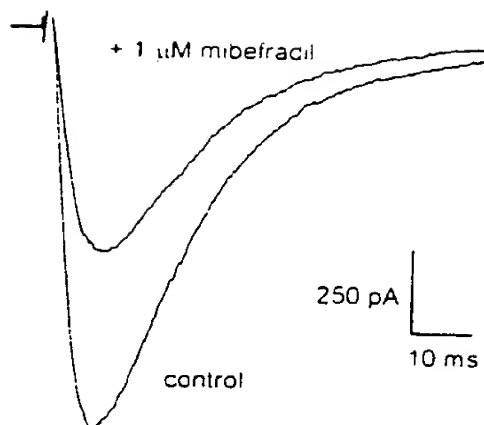


Figure 5A

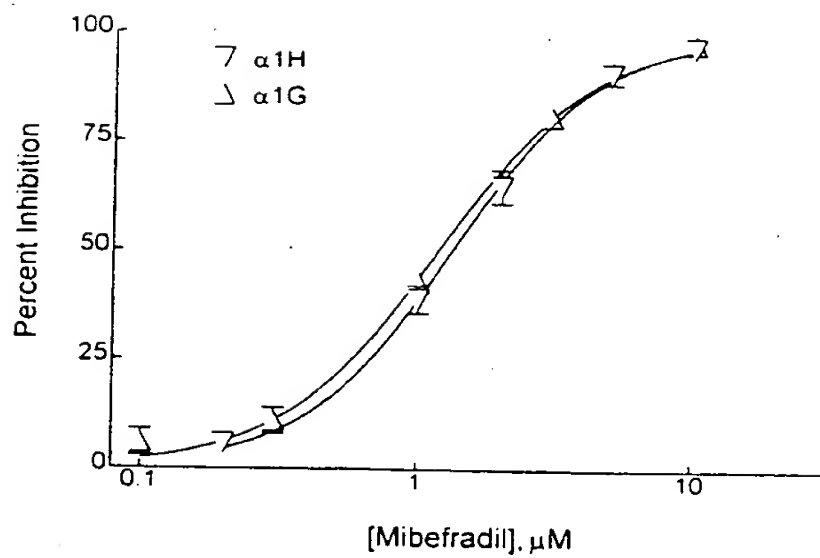


Figure 5B

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<110> Perez-Reyes, Edward  
 Cribbs, Leanne L.  
 Loyola University of Chicago

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	385					390					395					400	
5	acc	aag	cag	cgg	gaa	agc	cag	ctg	atg	cgg	gag	cag	cgt	gtg	cgg	ttc	1248
	Thr	Lys	Gln	Arg	Glu	Ser	Gln	Leu	Met	Arg	Glu	Gln	Arg	Val	Arg	Phe	
					405					410					415		
10	ctg	tcc	aac	gcc	agc	acc	ctg	gct	agc	ttc	tct	gag	ccc	ggc	agc	tgc	1296
	Leu	Ser	Asn	Ala	Ser	Thr	Leu	Ala	Ser	Phe	Ser	Glu	Pro	Gly	Ser	Cys	
				420					425					430			
15	tat	gag	gag	ctg	ctc	aag	tac	ctg	gtg	tac	atc	ctt	cgt	aag	gca	gcc	1344
	Tyr	Glu	Glu	Leu	Leu	Lys	Tyr	Leu	Val	Tyr	Ile	Leu	Arg	Lys	Ala	Ala	
			435					440					445				
20	cgc	agg	ctg	gct	cag	gtc	tct	cgg	gca	gca	ggg	gtg	cgg	gtt	ggg	ctg	1392
	Arg	Arg	Leu	Ala	Gln	Val	Ser	Arg	Ala	Ala	Gly	Val	Arg	Val	Gly	Leu	
		450					455					460					
25	ctc	agc	agc	cca	gca	ccc	ctc	ggg	ggc	cag	gag	acc	cag	ccc	agc	agc	1440
	Leu	Ser	Ser	Pro	Ala	Pro	Leu	Gly	Gly	Gln	Glu	Thr	Gln	Pro	Ser	Ser	
		465				470				475						480	
30	agc	tgc	tct	cgc	tcc	cac	cgc	cgc	cta	tcc	gtc	cac	cac	ctg	gtg	cac	1488
	Ser	Cys	Ser	Arg	Ser	His	Arg	Arg	Leu	Ser	Val	His	His	Leu	Val	His	
					485					490					495		
35	cac	cac	cac	cac	cat	cac	cac	cac	tac	cac	ctg	ggc	aat	ggg	acg	ctc	1536
	His	His	His	His	His	His	His	His	Tyr	His	Leu	Gly	Asn	Gly	Thr	Leu	
				500					505					510			
40	agg	gcc	ccc	cgg	gcc	agc	ccg	gag	atc	cag	gac	agg	gat	gcc	aat	ggg	1584
	Arg	Ala	Pro	Arg	Ala	Ser	Pro	Glu	Ile	Gln	Asp	Arg	Asp	Ala	Asn	Gly	
			515					520					525				
45	tcc	cgc	cgg	ctc	atg	ctg	cca	cca	ccc	tgc	acg	cct	gcc	ctc	tcc	ggg	1632
	Ser	Arg	Arg	Leu	Met	Leu	Pro	Pro	Pro	Ser	Thr	Pro	Ala	Leu	Ser	Gly	
		530					535					540					
50	gcc	ccc	cct	ggt	ggc	gca	gag	tct	gtg	cac	agc	ttc	tac	cat	gcc	gac	1680
	Ala	Pro	Pro	Gly	Gly	Ala	Glu	Ser	Val	His	Ser	Phe	Tyr	His	Ala	Asp	
		545				550				555						560	
55	tgc	cac	tta	gag	cca	gtc	cgc	tgc	cag	gcg	ccc	cct	ccc	agg	tcc	cca	1728
	Cys	His	Leu	Glu	Pro	Val	Arg	Cys	Gln	Ala	Pro	Pro	Pro	Arg	Ser	Pro	
					565				570						575		
60	tct	gag	gca	tcc	ggc	agg	act	gtg	ggc	agc	ggg	aag	gtg	tat	ccc	acc	1776
	Ser	Glu	Ala	Ser	Gly	Arg	Thr	Val	Gly	Ser	Gly	Lys	Val	Tyr	Pro	Thr	
				580					585					590			
65	gtg	cac	acc	agc	cct	cca	ccg	gag	acg	ctg	aag	gag	aag	gca	cta	gta	1824
	Val	His	Thr	Ser	Pro	Pro	Pro	Glu	Thr	Leu	Lys	Glu	Lys	Ala	Leu	Val	
			595					600					605				
70	gag	gtg	gct	gcc	agc	tct	ggg	ccc	cca	acc	ctc	acc	agc	ctc	aac	atc	1872
	Glu	Val	Ala	Ala	Ser	Ser	Gly	Pro	Pro	Thr	Leu	Thr	Ser	Leu	Asn	Ile	
			610				615					620					
75	cca	ccc	ggg	ccc	tac	agc	tcc	atg	cac	aag	ctg	ctg	gag	aca	cag	agt	1920
	Pro	Pro	Gly	Pro	Tyr	Ser	Ser	Met	His	Lys	Leu	Leu	Glu	Thr	Gln	Ser	
						630					635					640	
80	aca	ggg	ggc	tgc	caa	agc	tct	tgc	aag	atc	tcc	agc	cct	tgc	ttg	aaa	1968

	Thr	Gly	Ala	Cys	Gln	Ser	Ser	Cys	Lys	Ile	Ser	Ser	Pro	Cys	Leu	Lys	
					645					650					655		
5	gca	gac	agt	gga	gcc	tgt	ggg	cca	gac	agc	tgc	ccc	tac	tgt	gcc	cgg	2016
	Ala	Asp	Ser	Gly	Ala	Cys	Gly	Pro	Asp	Ser	Cys	Pro	Tyr	Cys	Ala	Arg	
				660				665					670				
10	gcc	ggg	gca	ggg	gag	gtg	gag	ctc	gcc	gac	cgt	gaa	atg	cct	gac	tca	2064
	Ala	Gly	Ala	Gly	Glu	Val	Glu	Leu	Ala	Asp	Arg	Glu	Met	Pro	Asp	Ser	
				675				680					685				
15	gac	agc	gag	gca	gtt	tat	gag	ttc	aca	cag	gat	gcc	cag	cac	agc	gac	2112
	Asp	Ser	Glu	Ala	Val	Tyr	Glu	Phe	Thr	Gln	Asp	Ala	Gln	His	Ser	Asp	
				690			695					700					
	ctc	cgg	gac	ccc	cac	agc	cgg	cgg	caa	cgg	agc	ctg	ggc	cca	gat	gca	2160
	Leu	Arg	Asp	Pro	His	Ser	Arg	Arg	Gln	Arg	Ser	Leu	Gly	Pro	Asp	Ala	
				705		710				715						720	
20	gag	ccc	agc	tct	gtg	ctg	gcc	ttc	tgg	agg	cta	atc	tgt	gac	acc	ttc	2208
	Glu	Pro	Ser	Ser	Val	Leu	Ala	Phe	Trp	Arg	Leu	Ile	Cys	Asp	Thr	Phe	
					725				730						735		
25	cga	aag	att	gtg	gac	agc	aag	tac	ttt	ggc	cgg	gga	atc	atg	atc	gcc	2256
	Arg	Lys	Ile	Val	Asp	Ser	Lys	Tyr	Phe	Gly	Arg	Gly	Ile	Met	Ile	Ala	
				740				745						750			
30	atc	ctg	gtc	aac	aca	ctc	agc	atg	ggc	atc	gaa	tac	cac	gag	cag	ccc	2304
	Ile	Leu	Val	Asn	Thr	Leu	Ser	Met	Gly	Ile	Glu	Tyr	His	Glu	Gln	Pro	
				755				760					765				
35	gag	gag	ctt	acc	aac	gcc	cta	gaa	atc	agc	aac	atc	gtc	ttc	acc	agc	2352
	Glu	Glu	Leu	Thr	Asn	Ala	Leu	Glu	Ile	Ser	Asn	Ile	Val	Phe	Thr	Ser	
				770			775					780					
	ctc	ttt	gcc	ctg	gag	atg	ctg	ctg	aag	ctg	ctt	gtg	tat	ggg	ccc	ttt	2400
	Leu	Phe	Ala	Leu	Glu	Met	Leu	Leu	Lys	Leu	Leu	Val	Tyr	Gly	Pro	Phe	
					785	790				795					800		
40	ggc	tac	atc	aag	aat	ccc	tac	aac	atc	ttc	gat	ggg	gtc	att	gtg	gtc	2448
	Gly	Tyr	Ile	Lys	Asn	Pro	Tyr	Asn	Ile	Phe	Asp	Gly	Val	Ile	Val	Val	
					805					810					815		
45	atc	agc	gtg	tgg	gag	atc	gtg	ggc	cag	cag	ggg	ggc	ggc	ctg	tgc	gtg	2496
	Ile	Ser	Val	Trp	Glu	Ile	Val	Gly	Gln	Gln	Gly	Gly	Gly	Leu	Ser	Val	
				820				825						830			
50	ctg	cgg	acc	ttc	cgc	ctg	atg	cgt	gtg	ctg	aag	ctg	gtg	cgc	ttc	ctg	2544
	Leu	Arg	Thr	Phe	Arg	Leu	Met	Arg	Val	Leu	Lys	Leu	Val	Arg	Phe	Leu	
				835				840					845				
55	ccg	gcg	ctg	cag	cgg	cag	ctg	gtg	gtg	ctc	atg	aag	acc	atg	gac	aac	2592
	Pro	Ala	Leu	Gln	Arg	Gln	Leu	Val	Val	Leu	Met	Lys	Thr	Met	Asp	Asn	
				850			855					860					
	gtg	gcc	acc	ttc	tgc	atg	ctg	ctt	atg	ctc	ttc	atc	ttc	atc	ttc	agc	2640
	Val	Ala	Thr	Phe	Cys	Met	Leu	Leu	Met	Leu	Phe	Ile	Phe	Ile	Phe	Ser	
					865	870				875						880	
60	atc	ctg	ggc	atg	cat	ctc	ttc	ggc	tgc	aag	ttt	gcc	tct	gag	cgg	gat	2688
	Ile	Leu	Gly	Met	His	Leu	Phe	Gly	Cys	Lys	Phe	Ala	Ser	Glu	Arg	Asp	
					885					890					895		
	ggg	gac	acc	ctg	cca	gac	cgg	aag	aat	ttt	gac	tcc	ttg	ctc	tgg	gcc	2736



	Gly	Asp	Thr	Leu	Pro	Asp	Arg	Lys	Asn	Phe	Asp	Ser	Leu	Leu	Trp	Ala	
				900					905					910			
5	atc	gtc	act	gtc	ttt	cag	atc	ctg	acc	cag	gag	gac	tgg	aac	aaa	gtc	2784
	Ile	Val	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gln	Glu	Asp	Trp	Asn	Lys	Val	
			915					920					925				
10	ctc	tac	aat	ggg	atg	gcc	tcc	acg	tgc	tcc	tgg	gcg	gcc	ctt	tat	ttc	2332
	Leu	Tyr	Asn	Gly	Met	Ala	Ser	Thr	Ser	Ser	Trp	Ala	Ala	Leu	Tyr	Phe	
			930				935					940					
15	att	gcc	ctc	atg	acc	ttc	ggc	aac	tac	gtg	ctc	ttc	aat	ttg	ctg	gtc	2880
	Ile	Ala	Leu	Met	Thr	Phe	Gly	Asn	Tyr	Val	Leu	Phe	Asn	Leu	Leu	Val	
	945					950					955					960	
	gcc	att	ctg	gtg	gag	ggc	ttc	cag	gcg	gag	gga	gat	gcc	aac	aag	tcc	2928
	Ala	Ile	Leu	Val	Glu	Gly	Phe	Gln	Ala	Glu	Gly	Asp	Ala	Asn	Lys	Ser	
					965					970					975		
20	gaa	tca	gag	ccc	gat	ttc	ttc	tca	ccc	agc	ctg	gat	ggg	gat	ggg	gac	2976
	Glu	Ser	Glu	Pro	Asp	Phe	Phe	Ser	Pro	Ser	Leu	Asp	Gly	Asp	Gly	Asp	
				980					985					990			
25	agg	aag	aag	tgc	ttg	gcc	ttg	gtg	tcc	ctg	gga	gag	cac	ccg	gag	ctg	3024
	Arg	Lys	Lys	Cys	Leu	Ala	Leu	Val	Ser	Leu	Gly	Glu	His	Pro	Glu	Leu	
			995					1000					1005				
30	cgg	aag	agc	ctg	ctg	ccg	cct	ctc	atc	atc	cac	acg	gcc	gcc	aca	ccc	3072
	Arg	Lys	Ser	Leu	Leu	Pro	Pro	Leu	Ile	Ile	His	Thr	Ala	Ala	Thr	Pro	
	1010					1015						1020					
35	atg	tgc	ctg	ccc	aag	agc	acc	agc	acg	ggc	ctg	ggc	gag	gcg	ctg	ggc	3120
	Met	Ser	Leu	Pro	Lys	Ser	Thr	Ser	Thr	Gly	Leu	Gly	Glu	Ala	Leu	Gly	
	1025				1030					1035						1040	
	cct	gcg	tgc	cgc	cgc	acc	agc	agc	agc	ggg	tgc	gca	gag	cct	ggg	gcg	3168
	Pro	Ala	Ser	Arg	Arg	Thr	Ser	Ser	Ser	Gly	Ser	Ala	Glu	Pro	Gly	Ala	
				1045						1050					1055		
40	gcc	cac	gag	atg	aag	tca	ccg	ccc	agc	gcc	cgc	agc	tct	ccg	cac	agc	3216
	Ala	His	Glu	Met	Lys	Ser	Pro	Pro	Ser	Ala	Arg	Ser	Ser	Pro	His	Ser	
				1060				1065						1070			
45	ccc	tgg	agc	gct	gca	agc	agc	tgg	acc	agc	agg	cgc	tcc	agc	cgg	aac	3264
	Pro	Trp	Ser	Ala	Ala	Ser	Ser	Trp	Thr	Ser	Arg	Arg		Ser	Arg	Asn	
			1075					1080					1085				
50	agc	ctc	ggc	cgt	gca	ccc	agc	ctg	aag	cgg	aga	agc	cca	agt	gga	gag	3312
	Ser	Leu	Gly	Arg	Ala	Pro	Ser	Leu	Lys	Arg	Arg	Ser	Pro	Ser	Gly	Glu	
	1090					1095						1100					
55	cgg	cgg	tcc	ctg	ttg	tgc	gga	gaa	ggc	cag	gag	agc	cag	gat	gaa	gag	3360
	Arg	Arg	Ser	Leu	Leu	Ser	Gly	Glu	Gly	Gln	Glu	Ser	Gln	Asp	Glu	Glu	
	1105				1110					1115					1120		
	gag	agc	tca	gaa	gag	gag	cgg	gcc	agc	cct	gcg	ggc	agt	gac	cat	cgc	3408
	Glu	Ser	Ser	Glu	Glu	Glu	Arg	Ala	Ser	Pro	Ala	Gly	Ser	Asp	His	Arg	
				1125				1130						1135			
60	cac	agg	ggg	tcc	ctg	gag	cgg	gag	gcc	aag	agt	tcc	ttt	gac	ctg	cca	3456
	His	Arg	Gly	Ser	Leu	Glu	Arg	Glu	Ala	Lys	Ser	Ser	Phe	Asp	Leu	Pro	
			1140					1145						1150			
	gac	aca	ctg	cag	gtg	cca	ggg	ctg	cat	cgc	act	gcc	agt	ggc	cga	ggg	3504

	Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly Arg Gly	
	1155 1160 1165	
5	tct gct tct gag cac cag gac tgc aat ggc aag tgc gct tca ggg cgc Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser Gly Arg	3552
	1170 1175 1180	
10	ctg gcc cgg gcc ctg cgg cct gat gac ccc cca ctg gat ggg gat gac Leu Ala Arg Ala Leu Arg Pro Asp Asp Pro Pro Leu Asp Gly Asp Asp	3600
	1185 1190 1195 1200	
15	gcc gat gac gag ggc aac ctg agc aaa ggg gaa cgg gtc cgc gcg tgg Ala Asp Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Val Arg Ala Trp	3648
	1205 1210 1215	
	atc cga gcc cga ctc cct gcc tgc tgc ctc gag cga gac tcc tgg tca Ile Arg Ala Arg Leu Pro Ala Cys Cys Leu Glu Arg Asp Ser Trp Ser	3696
	1220 1225 1230	
20	gcc tac atc ttc cct cct cag tcc agg ttc cgc ctc ctg tgt cac cgg Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys His Arg	3744
	1235 1240 1245	
25	atc atc acc cac aag atg ttc gac cac gtg gtc ctt gtc atc atc ttc Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile Ile Phe	3792
	1250 1255 1260	
30	ctt aac tgc atc acc atc gcc atg gag cgc ccc aaa att gac ccc cac Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp Pro His	3840
	1265 1270 1275 1280	
35	agc gct gaa cgc atc ttc ctg acc ctc tcc aat tac atc ttc acc gca Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe Thr Ala	3888
	1285 1290 1295	
	gtc ttt ctg gct gaa atg aca gtg aag gtg gtg gca ctg ggc tgg tgc Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly Trp Cys	3936
	1300 1305 1310	
40	ttc ggg gag cag gcg tac ctg cgg agc agt tgg aac gtg ctg gac ggg Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu Asp Gly	3984
	1315 1320 1325	
45	ctg ttg gtg ctc atc tcc gtc atc gac att ctg gtg tcc atg gtc tct Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met Val Ser	4032
	1330 1335 1340	
50	gac agc ggc acc aag atc ctg ggc atg ctg agg gtg ctg cgg ctg ctg Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg Leu Leu	4080
	1345 1350 1355 1360	
55	cgg acc ctg cgc ccg ctc agg gtg atc agc cgg gcg cag ggg ctg aag Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Gln Gly Leu Lys	4128
	1365 1370 1375	
	ctg gtg gtg gag acg ctg atg tcc tca ctg aaa ccc atc ggc aac att Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly Asn Ile	4176
	1380 1385 1390	
60	gta gtc atc tgc tgt gcc ttc ttc atc att ttc ggc atc ttg ggg gtg Val Val Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu Gly Val	4224
	1395 1400 1405	
	cag ctc ttc aaa ggg aag ttt ttc gtg tgc cag ggc gag gat acc agg	4272

	Gln	Leu	Phe	Lys	Gly	Lys	Phe	Phe	Val	Cys	Gln	Gly	Glu	Asp	Thr	Arg	
	1410						1415					1420					
5	aac	atc	acc	aat	aaa	tcg	gac	tgt	gcc	gag	gcc	agt	tac	cgg	tgg	gtc	4320
	Asn	Ile	Thr	Asn	Lys	Ser	Asp	Cys	Ala	Glu	Ala	Ser	Tyr	Arg	Trp	Val	
	1425					1430				1435					1440		
10	cgg	cac	aag	tac	aac	ttt	gac	aac	ctt	ggc	cag	gcc	ctg	atg	tcc	ctg	4368
	Arg	His	Lys	Tyr	Asn	Phe	Asp	Asn	Leu	Gly	Gln	Ala	Leu	Met	Ser	Leu	
					1445					1450					1455		
15	ttc	gtt	ttg	gcc	tcc	aag	gat	ggt	tgg	gtg	gac	atc	atg	tac	gat	ggg	4416
	Phe	Val	Leu	Ala	Ser	Lys	Asp	Gly	Trp	Val	Asp	Ile	Met	Tyr	Asp	Gly	
				1460					1465					1470			
20	ctg	gat	gct	gtg	ggc	gtg	gac	cag	cag	ccc	atc	atg	aac	cac	aac	ccc	4464
	Leu	Asp	Ala	Val	Gly	Val	Asp	Gln	Gln	Pro	Ile	Met	Asn	His	Asn	Pro	
				1475				1480					1485				
25	tgg	atg	ctg	ctg	tac	ttc	atc	tcg	ttc	ctg	ctc	att	gtg	gcc	ttc	ttt	4512
	Trp	Met	Leu	Leu	Tyr	Phe	Ile	Ser	Phe	Leu	Leu	Ile	Val	Ala	Phe	Phe	
		1490					1495					1500					
30	gtc	ctg	aac	atg	ttt	gtg	ggt	gtg	gtg	gtg	gag	aac	ttc	cac	aag	tgt	4560
	Val	Leu	Asn	Met	Phe	Val	Gly	Val	Val	Val	Glu	Asn	Phe	His	Lys	Cys	
	1505					1510					1515					1520	
35	cgg	cag	cac	cag	gag	gaa	gag	gag	gcc	cgg	cgg	cgg	gag	gag	aag	cgc	4608
	Arg	Gln	His	Gln	Glu	Glu	Glu	Glu	Ala	Arg	Arg	Arg	Glu	Glu	Lys	Arg	
					1525				1530						1535		
40	cta	cga	aga	ctg	gag	aaa	aag	aga	agg	agt	aag	gag	aag	cag	atg	gct	4656
	Leu	Arg	Arg	Leu	Glu	Lys	Lys	Arg	Arg	Ser	Lys	Glu	Lys	Gln	Met	Ala	
				1540					1545					1550			
45	gaa	gcc	cag	tgc	aaa	cct	tac	tac	tcc	gac	tac	tcc	cgc	ttc	cgg	ctc	4704
	Glu	Ala	Gln	Cys	Lys	Pro	Tyr	Tyr	Ser	Asp	Tyr	Ser	Arg	Phe	Arg	Leu	
		1555						1560					1565				
50	ctc	gtc	cac	cac	ttg	tgc	acc	agc	cac	tac	ctg	gac	ctc	ttc	atc	aca	4752
	Leu	Val	His	His	Leu	Cys	Thr	Ser	His	Tyr	Leu	Asp	Leu	Phe	Ile	Thr	
		1570					1575					1580					
55	ggt	gtc	atc	ggg	ctg	aac	gtg	gtc	acc	atg	gcc	atg	gag	cac	tac	cag	4800
	Gly	Val	Ile	Gly	Leu	Asn	Val	Val	Thr	Met	Ala	Met	Glu	His	Tyr	Gln	
	1585				1590					1595						1600	
60	cag	ccc	cag	att	ctg	gat	gag	gct	ctg	aag	atc	tgc	aac	tac	atc	ttc	4848
	Gln	Pro	Gln	Ile	Leu	Asp	Glu	Ala	Leu	Lys	Ile	Cys	Asn	Tyr	Ile	Phe	
				1605					1610					1615			
65	act	gtc	atc	ttt	gtc	ttg	gag	tca	gtt	ttc	aaa	ctt	gtg	gcc	ttt	ggt	4896
	Thr	Val	Ile	Phe	Val	Leu	Glu	Ser	Val	Phe	Lys	Leu	Val	Ala	Phe	Gly	
				1620					1625					1630			
70	ttc	cgt	cgg	ttc	ttc	cag	gac	agg	tgg	aac	cag	ctg	gac	ctg	gcc	att	4944
	Phe	Arg	Arg	Phe	Phe	Gln	Asp	Arg	Trp	Asn	Gln	Leu	Asp	Leu	Ala	Ile	
		1635					1640					1645					
75	gtg	ctg	ctg	tcc	atc	atg	ggc	atc	acg	ctg	gag	gaa	atc	gag	gtc	aac	4992
	Val	Leu	Leu	Ser	Ile	Met	Gly	Ile	Thr	Leu	Glu	Glu	Ile	Glu	Val	Asn	
		1650					1655					1660					
80	gcc	tcg	ctg	ccc	atc	aac	ccc	acc	atc	atc	cgc	atc	atg	agg	gtg	ctg	5040

	Ala	Ser	Leu	Pro	Ile	Asn	Pro	Thr	Ile	Ile	Arg	Ile	Met	Arg	Val	Leu	
	1665					1670					1675					1680	
5	cgc	att	gcc	cga	gtg	ctg	aag	ctg	ctg	aag	atg	gct	gtg	ggc	atg	cgg	5088
	Arg	Ile	Ala	Arg	Val	Leu	Lys	Leu	Leu	Lys	Met	Ala	Val	Gly	Met	Arg	
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15	tat gag gag ctg ctc aag tac ctg gtg tac atc ctt cgt aag gca gcc Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala	435	440	445	1344
20	cgc agg ctg gct cag gtc tct cgg gca gca ggt gtg cgg gtt ggg ctg Arg Arg Leu Ala Gln Val Ser Arg Ala Ala Gly Val Arg Val Gly Leu	450	455	460	1392
25	ctc agc agc cca gca ccc ctc ggg ggc cag gag acc cag ccc agc agc Leu Ser Ser Pro Ala Pro Leu Gly Gly Gln Glu Thr Gln Pro Ser Ser	465	470	475	1440
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35	cac cac cac cac cat cac cac cac tac cac ctg ggc aat ggg acg ctc His His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu	500	505	510	1536
40	agg gcc ccc cgg gcc agc ccg gag atc cag gac agg gat gcc aat ggg Arg Ala Pro Arg Ala Ser Pro Glu Ile Gln Asp Arg Asp Ala Asn Gly	515	520	525	1584
45	tcc cgc cgg ctc atg ctg cca cca ccc tgc acg cct gcc ctc tcc ggg Ser Arg Arg Leu Met Leu Pro Pro Pro Ser Thr Pro Ala Leu Ser Gly	530	535	540	1632
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60	tct gag gca tcc ggc agg act gtg ggc agc ggg aag gtg tat ccc acc Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys Val Tyr Pro Thr	580	585	590	1776
65	gtg cac acc agc cct cca ccg gag acg ctg aag gag aag gca cta gta Val His Thr Ser Pro Pro Pro Glu Thr Leu Lys Glu Lys Ala Leu Val	595	600	605	1824
70	gag gtg gct gcc agc tct ggg ccc cca acc ctc acc agc ctc aac atc Glu Val Ala Ala Ser Ser Gly Pro Pro Thr Leu Thr Ser Leu Asn Ile	610	615	620	1872
75	cca ccc ggg ccc tac agc tcc atg cac aag ctg ctg gag aca cag agt Pro Pro Gly Pro Tyr Ser Ser Met His Lys Leu Leu Glu Thr Gln Ser	625	630	635	1920
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	Ile	Leu	Val	Asn	Thr	Leu	Ser	Met	Gly	Ile	Glu	Tyr	His	Glu	Gln	Pro	
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40	gag	gag	ctt	acc	aac	gcc	cta	gaa	atc	agc	aac	atc	gtc	ttc	acc	agc	2352
	Glu	Glu	Leu	Thr	Asn	Ala	Leu	Glu	Ile	Ser	Asn	Ile	Val	Phe	Thr	Ser	
		770					775					780					
45	ctc	ttt	gcc	ctg	gag	atg	ctg	ctg	aag	ctg	ctt	gtg	tat	ggc	ccc	ttt	2400
	Leu	Phe	Ala	Leu	Glu	Met	Leu	Leu	Lys	Leu	Leu	Val	Tyr	Gly	Pro	Phe	
	785					790					795					800	
50	ggc	tac	atc	aag	aat	ccc	tac	aac	atc	ttc	gat	ggc	gtc	att	gtg	gtc	2448
	Gly	Tyr	Ile	Lys	Asn	Pro	Tyr	Asn	Ile	Phe	Asp	Gly	Val	Ile	Val	Val	
					805				810						815		
55	atc	agc	gtg	tgg	gag	atc	gtg	ggc	cag	cag	ggg	ggc	ggc	ctg	tcg	gtg	2496
	Ile	Ser	Val	Trp	Glu	Ile	Val	Gly	Gln	Gly	Gly	Gly	Gly	Leu	Ser	Val	
				820				825					830				
60	ctg	cgg	acc	ttc	cgc	ctg	atg	cgt	gtg	ctg	aag	ctg	gtg	cgc	ttc	ctg	2544
	Leu	Arg	Thr	Phe	Arg	Leu	Met	Arg	Val	Leu	Lys	Leu	Val	Arg	Phe	Leu	
				835				840					845				
65	ccg	gcg	ctg	cag	cgg	cag	ctg	gtg	gtg	ctc	atg	aag	acc	atg	gac	aac	2592
	Pro	Ala	Leu	Gln	Arg	Gln	Leu	Val	Val	Leu	Met	Lys	Thr	Met	Asp	Asn	
		850					855					860					
70	gtg	gcc	acc	ttc	tgc	atg	ctg	ctt	atg	ctc	ttc	atc	ttc	atc	ttc	agc	2640
	Val	Ala	Thr	Phe	Cys	Met	Leu	Leu	Met	Leu	Phe	Ile	Phe	Ile	Phe	Ser	
	865					870					875					880	
75	atc	ctg	ggc	atg	cat	ctc	ttc	ggc	tgc	aag	ttt	gcc	tct	gag	cgg	gat	2688
	Ile	Leu	Gly	Met	His	Leu	Phe	Gly	Cys	Lys	Phe	Ala	Ser	Glu	Arg	Asp	
					885					890					895		
80	ggg	gac	acc	ctg	cca	gac	cgg	aag	aat	ttt	gac	tcc	ttg	ctc	tgg	gcc	2736
	Gly	Asp	Thr	Leu	Pro	Asp	Arg	Lys	Asn	Phe	Asp	Ser	Leu	Leu	Trp	Ala	

	900	905	910	
5	atc gtc act gtc ttt cag atc ctg acc cag gag gac tgg aac aas gtc Ile Val Thr Val Phe Gln Ile Leu Thr Gln Glu Asp Trp Asn Lys Val 915 920 925	2784		
10	ctc tac aat ggt atg gcc tcc acg tcg tcc tgg gcg gcc ctt tat ttc Leu Tyr Asn Gly Met Ala Ser Thr Ser Ser Trp Ala Ala Leu Tyr Phe 930 935 940	2832		
15	att gcc ctc atg acc ttc ggc aac tac gtg ctc ttc aat ttg ctg gtc Ile Ala Leu Met Thr Phe Gly Asn Tyr Val Leu Phe Asn Leu Leu Val 945 950 955 960	2880		
20	gcc att ctg gtg gag ggc ttc cag gcg gag gga gat gcc aac aag tcc Ala Ile Leu Val Glu Gly Phe Gln Ala Glu Gly Asp Ala Asn Lys Ser 965 970 975	2928		
25	gaa tca gag ccc gat ttc ttc tca ccc agc ctg gat ggt gat ggg gac Glu Ser Glu Pro Asp Phe Phe Ser Pro Ser Leu Asp Gly Asp Gly Asp 980 985 990	2976		
30	agg aag aag tgc ttg gcc ttg gtg tcc ctg gga gag cac ccg gag ctg Arg Lys Lys Cys Leu Ala Leu Val Ser Leu Gly Glu His Pro Glu Leu 995 1000 1005	3024		
35	cgg aag agc ctg ctg ccg cct ctc atc atc cac acg gcc gcc aca ccc Arg Lys Ser Leu Leu Pro Pro Leu Ile Ile His Thr Ala Ala Thr Pro 1010 1015 1020	3072		
40	atg tcg ctg ccc aag agc acc agc acg ggc ctg ggc gag gcg ctg ggc Met Ser Leu Pro Lys Ser Thr Ser Thr Gly Leu Gly Glu Ala Leu Gly 1025 1030 1035 1040	3120		
45	cct gcg tcg cgc cgc acc agc agc agc ggc tcg gca gag cct ggg gcg Pro Ala Ser Arg Thr Ser Ser Ser Gly Ser Ala Glu Pro Gly Ala 1045 1050 1055	3168		
50	gcc cac gag atg aag tca ccg ccc agc gcc cgc agc tct ccg cac agc Ala His Glu Met Lys Ser Pro Pro Ser Ala Arg Ser Ser Pro His Ser 1060 1065 1070	3216		
55	ccc tgg agc gct gca agc agc tgg acc agc agg cgc tcc agc cgg aac Pro Trp Ser Ala Ala Ser Ser Trp Thr Ser Arg Arg Ser Ser Arg Asn 1075 1080 1085	3264		
60	agc ctc ggc cgt gca ccc agc ctg aag cgg aga agc cca agt gga gag Ser Leu Gly Arg Ala Pro Ser Leu Lys Arg Arg Ser Pro Ser Gly Glu 1090 1095 1100	3312		
65	cgg cgg tcc ctg ttg tcg gga gaa ggc cag gag agc cag gat gaa gag Arg Arg Ser Leu Leu Ser Gly Glu Gly Gln Glu Ser Gln Asp Glu Glu 1105 1110 1115 1120	3360		
70	gag agc tca gaa gag gag cgg gcc agc cct gcg ggc agt gac cat cgc Glu Ser Ser Glu Glu Glu Arg Ala Ser Pro Ala Gly Ser Asp His Arg 1125 1130 1135	3408		
75	cac agg ggg tcc ctg gag cgg gag gcc aag agt tcc ttt gac ctg cca His Arg Gly Ser Leu Glu Arg Glu Ala Lys Ser Ser Phe Asp Leu Pro 1140 1145 1150	3456		
80	gac aca ctg cag gtg cca ggg ctg cat cgc act gcc agt ggc cga ggg Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly Arg Gly 1155 1160 1165 1170	3504		

	1155	1160	1165	
5	tct gct tct gag cac cag gac tgc aat ggc aag tgc gct tca ggg cgc Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser Gly Arg 1170 1175 1180	3552		
10	ctg gcc cgg gcc ctg cgg cct gat gac ccc cca ctg gat ggg gat gac Leu Ala Arg Ala Leu Arg Pro Asp Asp Pro Pro Leu Asp Gly Asp Asp 1185 1190 1195 1200	3600		
15	gcc gat gac gag ggc aac ctg agc aaa ggg gaa cgg gtc cgc gcg tgg Ala Asp Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Val Arg Ala Trp 1205 1210 1215	3648		
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25	gcc tac atc ttc cct cct cag tcc agg ttc cgc ctc ctg tgt cac cgg Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys His Arg 1235 1240 1245	3744		
30	atc atc acc cac aag atg ttc gac cac gtg gtc ctt gtc atc atc ttc Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile Ile Phe 1250 1255 1260	3792		
35	ctt aac tgc atc acc atc gcc atg gag cgc ccc aaa att gac ccc cac Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp Pro His 1265 1270 1275 1280	3840		
40	agc gct gaa cgc atc ttc ctg acc ctc tcc aat tac atc ttc acc gca Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe Thr Ala 1285 1290 1295	3888		
45	gtc ttt ctg gct gaa atg aca gtg aag gtg gtg gca ctg ggc tgg tgc Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly Trp Cys 1300 1305 1310	3936		
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	1410	1415	1420	
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10	cgg cac aag tac aac ttt gac aac ctt ggc cag gcc ctg atg tcc ctg Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met Ser Leu 1445 1450 1455			4368
15	ttc gtt ttg gcc tcc aag gat ggt tgg gtg gac atc atg tac gat ggg Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr Asp Gly 1460 1465 1470			4416
20	ctg gat gct gtg ggc gtg gac cag cag ccc atc atg aac cac aac ccc Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His Asn Pro 1475 1480 1485			4464
25	tgg atg ctg ctg tac ttc atc tcg ttc ctg ctc att gtg gcc ttc ttt Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala Phe Phe 1490 1495 1500			4512
30	gtc ctg aac atg ttt gtg ggt gtg gtg gtg gag aac ttc cac aag tgt Val Leu Asn Met Phe Val Gly Val Val Val Glu Asn Phe His Lys Cys 1505 1510 1515 1520			4560
35	cgg cag cac cag gag gaa gag gag gcc cgg cgg cgg gag gag aag cgc Arg Gln His Gln Glu Glu Glu Glu Ala Arg Arg Arg Glu Glu Lys Arg 1525 1530 1535			4608
40	cta cga aga ctg gag aaa aag aga agg aat cta atg ctg gac gat gta Leu Arg Arg Leu Glu Lys Lys Arg Arg Asn Leu Met Leu Asp Asp Val 1540 1545 1550			4656
45	att gct tcc ggc agc tca gcc agc gct gcg tca gaa gcc cag tgc aaa Ile Ala Ser Gly Ser Ser Ala Ser Ala Ala Ser Glu Ala Gln Cys Lys 1555 1560 1565			4704
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	1665	1670	1675	1680	
5	aac ccc acc atc atc cgc atc atg agg gtg ctg cgc att gcc cga gtg Asn Pro Thr Ile Ile Arg Ile Met Arg Val Leu Arg Ile Ala Arg Val	1685	1690	1695	5086
10	ctg aag ctg ctg aag atg gct gtg ggc atg cgg gcg ctg ctg gac acg Leu Lys Leu Leu Lys Met Ala Val Gly Met Arg Ala Leu Leu Asp Thr	1700	1705	1710	5136
15	gtg atg cag gcc ctg ccc cag gtg ggg aac ctg gga ctt ctc ttc atg Val Met Gln Ala Leu Pro Gln Val Gly Asn Leu Gly Leu Leu Phe Met	1715	1720	1725	5184
20	ttg ttg ttt ttc atc ttt gca gct ctg ggc gtg gag ctc ttt gga gac Leu Leu Phe Phe Ile Phe Ala Leu Gly Val Glu Leu Phe Gly Asp	1730	1735	1740	5232
25	ctg gag tgt gac gag aca cac ccc tgt gag ggc ctg ggc cgt cat gcc Leu Glu Cys Asp Glu Thr His Pro Cys Glu Gly Leu Gly Arg His Ala	1745	1750	1755	5280
30	acc ttt cgg aac ttt ggc atg gcc ttc cta acc ctc ttc cga gtc tcc Thr Phe Arg Asn Phe Gly Met Ala Phe Leu Thr Leu Phe Arg Val Ser	1765	1770	1775	5328
35	aca ggt gac aat tgg aat ggc att atg aag gac acc ctc cgg gac tgt Thr Gly Asp Asn Trp Asn Gly Ile Met Lys Asp Thr Leu Arg Asp Cys	1780	1785	1790	5376
40	gac cag gag tcc acc tgc tac aac acg gtc atc tcg cct atc tac ttt Asp Gln Glu Ser Thr Cys Tyr Asn Thr Val Ile Ser Pro Ile Tyr Phe	1795	1800	1805	5424
45	gtg tcc ttc gtg ctg acg gcc cag ttc gtg cta gtc aac gtg gtg atc Val Ser Phe Val Leu Thr Ala Gln Phe Val Leu Val Asn Val Val Ile	1810	1815	1820	5472
50	gcc gtg ctg atg aag cac ctg gag gag agc aac aag gag gcc aag gag Ala Val Leu Met Lys His Leu Glu Glu Ser Asn Lys Glu Ala Lys Glu	1825	1830	1835	5520
55	gag gcc gag cta gag gct gag ctg gag ctg gag atg aag acc ctc agc Glu Ala Glu Leu Glu Ala Glu Leu Glu Met Lys Thr Leu Ser	1845	1850	1855	5568
60	ccc cag ccc cac tcg cca ctg ggc agc ccc ttc ctc tgg cct ggg gtc Pro Gln Pro His Ser Pro Leu Gly Ser Pro Phe Leu Trp Pro Gly Val	1860	1865	1870	5616
65	gag ggc ccc gac agc ccc gac agc ccc aag cct ggg gct ctg cac cca Glu Gly Pro Asp Ser Pro Asp Ser Pro Lys Pro Gly Ala Leu His Pro	1875	1880	1885	5664
70	gcg gcc cac gcg aga tca gcc tcc cac ttt tcc ctg gag cac ccc acg Ala Ala His Ala Arg Ser Ala Ser His Phe Ser Leu Glu His Pro Thr	1890	1895	1900	5712
75	atg cag ccc cac ccc acg gag ctg cca gga cca gac tta ctg act gtg Met Gln Pro His Pro Thr Glu Leu Pro Gly Pro Asp Leu Leu Thr Val	1905	1910	1915	5760
80	cgg aag tct ggg gtc agc cga acg cac tct ctg ccc aat gac agc tac Arg Lys Ser Gly Val Ser Arg Thr His Ser Leu Pro Asn Asp Ser Tyr				5808

	1925	1930	1935	
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10	tgg ggg ctc ccc aaa gct cag tca ggc tcc gtc ttg tcc gtt cac tcc Trp Gly Leu Pro Lys Ala Gln Ser Gly Ser Val Leu Ser Val His Ser 1955 1960 1965	5904		
15	cag cca gca gat acc agc tac atc ctg cag ctt ccc aaa gat gca cct Gln Pro Ala Asp Thr Ser Tyr Ile Leu Gln Leu Pro Lys Asp Ala Pro 1970 1975 1980	5952		
20	cat ctg ctc cag ccc cac agc gcc cca acc tgg ggc acc atc ccc aaa His Leu Leu Gln Pro His Ser Ala Pro Thr Trp Gly Thr Ile Pro Lys 1985 1990 1995 2000	6000		
25	ctg ccc cca cca gga cgc tcc cct ttg gct cag agg cca ctc agg cgc Leu Pro Pro Pro Gly Arg Ser Pro Leu Ala Gln Arg Pro Leu Arg Arg 2005 2010 2015	6048		
30	cag gca gca ata agg act gac tcc ttg gac gtt cag ggt ctg ggc agc Gln Ala Ala Ile Arg Thr Asp Ser Leu Asp Val Gln Gly Leu Gly Ser 2020 2025 2030	6096		
35	cgg gaa gac ctg ctg gca gag gtg agt ggg ccc tcc ccg ccc ctg gcc Arg Glu Asp Leu Leu Ala Glu Val Ser Gly Pro Ser Pro Pro Leu Ala 2035 2040 2045	6144		
40	cgg gcc tac tct ttc tgg ggc cag tca agt acc cag gca cag cag cac Arg Ala Tyr Ser Phe Trp Gly Gln Ser Ser Thr Gln Ala Gln Gln His 2050 2055 2060	6192		
45	tcc cgc agc cac agc aag atc tcc aag cac atg acc ccg cca gcc cct Ser Arg Ser His Ser Lys Ile Ser Lys His Met Thr Pro Pro Ala Pro 2065 2070 2075 2080	6240		
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55	agc agc tta gag ttg gac acg gag ctg agc tgg att tca gga gac ctc Ser Ser Leu Glu Leu Asp Thr Glu Leu Ser Trp Ile Ser Gly Asp Leu 2100 2105 2110	6336		
60	ctg ccc cct ggc ggc cag gag gag ccc cca tcc cca cgg gac ctg aag Leu Pro Pro Gly Gly Gln Glu Glu Pro Pro Ser Pro Arg Asp Leu Lys 2115 2120 2125	6384		
65	aag tgc tac agc gtg gag gcc cag agc tgc cag cgc cgg cct acg tcc Lys Cys Tyr Ser Val Glu Ala Gln Ser Cys Gln Arg Arg Pro Thr Ser 2130 2135 2140	6432		
70	tgg ctg gat gag cag agg aga cac tct atc gcc gtc agc tgc ctg gac Trp Leu Asp Glu Gln Arg Arg His Ser Ile Ala Val Ser Cys Leu Asp 2145 2150 2155 2160	6480		
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80	cag cct ctt ggg ggg cct ggg agc cgg ccc aag aaa aaa ctc agc ccg Gln Pro Leu Gly Gly Pro Gly Ser Arg Pro Lys Lys Lys Leu Ser Pro 2180 2185 2190 2195	6576		

	2180	2185	2190	
5	cct agt atc acc ata gaa ccc ccc gag agc caa ggt cct cgg acc ccg Pro Ser Ile Thr Ile Asp Pro Pro Glu Ser Gln Gly Pro Arg Thr Pro 2195 2200 2205	6624		
10	ccc agc cct ggt atc tgc ctc cgg agg agg gct ccg tcc agc gac tcc Pro Ser Pro Gly Ile Cys Leu Arg Arg Arg Ala Pro Ser Ser Asp Ser 2210 2215 2220	6672		
15	aag gat ccc ttg gcc tct ggc ccc cct gac agc atg gct gcc tgg ccc Lys Asp Pro Leu Ala Ser Gly Pro Pro Asp Ser Met Ala Ala Ser Pro 2225 2230 2235 2240	6720		
20	tcc cca aag aaa gat gtg ctg agt ctc tcc ggt tta tcc tct gac cca Ser Pro Lys Lys Asp Val Leu Ser Leu Ser Gly Leu Ser Ser Asp Pro 2245 2250 2255	6768		
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45	ggg ccg ggg tca gca gaa aag gac ccg ggc agc gcg gac tcc gag gcg Gly Pro Gly Ser Ala Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala 35 40 45	144		
50	gag ggg ctg ccg tac ccg gcg ctg gcc ccg gtg gtt ttc ttc tac ttg Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu 50 55 60	192		
55	agc cag gac agc cgc ccg ccg agc tgg tgt ctc cgc acg gtc tgt aac Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn 65 70 75 80	240		
60	ccc tgg ttt gag cgc atc agc atg ttg gtc atc ctt ctc aac tgc gtg Pro Trp Phe Glu Arg Ile Ser Met Leu Val Ile Leu Leu Asn Cys Val 85 90 95	288		
65	acc ctg ggc atg ttc cgg cca tgc gag gac atc gcc tgt gac tcc cag Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln 100 105 110	336		
70	cgc tgc cgg atc ctg gag gcc ttt gat gac ttc atc ttt gcc ttc ttc Arg Cys Arg Ile Leu Gln Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe 115 120 125	384		

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	aag tgt tac ctg gga gac act tgg aac cgg ctt gac ttt ttc atc gtc 480 Lys Cys Tyr Leu Gly Asp Thr Trp Asn Arg Leu Asp Phe Phe Ile Val 145 150 155 160	
10	atc gca ggg atg ctg gag tac tgg ctg gac ctg cag aac gtc agc ttc 528 Ile Ala Gly Met Leu Glu Tyr Ser Leu Asp Leu Gln Asn Val Ser Phe 165 170 175	
	tca gct gtc agg aca gtc cgt gtg ctg cga ccg ctc agg gcc att aac 576 Ser Ala Val Arg Thr Val Arg Val Leu Arg Pro Leu Arg Ala Ile Asn 180 185 190	
20	cgg gtg ccc agc atg cgc atc ctt gtc acg ttg ctg ctg gat acg ctg 624 Arg Val Pro Ser Met Arg Ile Leu Val Thr Leu Leu Leu Asp Thr Leu 195 200 205	
	ccc atg ctg ggc aac gtc ctg ctg ctc tgc ttc ttc gtc ttc ttc atc 672 Pro Met Leu Gly Asn Val Leu Leu Leu Cys Phe Phe Val Phe Phe Ile 210 215 220	
25	ttc ggc atc gtc ggc gtc cag ctg tgg gca ggg ctg ctt cgg aac cga 720 Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg 225 230 235 240	
	tgc ttc cta cct gag aat ttc agc ctc ccc ctg agc gtg gac ctg gag 768 Cys Phe Leu Pro Glu Asn Phe Ser Leu Pro Leu Ser Val Asp Leu Glu 245 250 255	
35	cgc tat tac cag aca gag aac gag gat gag agc ccc ttc atc tgc tcc 816 Arg Tyr Tyr Gln Thr Glu Asn Glu Asp Glu Ser Pro Phe Ile Cys Ser 260 265 270	
	cag cca cgc gag aac ggc atg cgg tcc tgc aga agc gtg ccc acg ctg 864 Gln Pro Arg Glu Asn Gly Met Arg Ser Cys Arg Ser Val Pro Thr Leu 275 280 285	
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	tac aac agc tcc agc aac acc acc tgt gtc aac tgg aac cag tac tac 960 Tyr Asn Ser Ser Ser Asn Thr Thr Cys Val Asn Trp Asn Gln Tyr Tyr 305 310 315 320	
50	acc aac tgc tca gcg ggg gag cac aac ccc ttc aag ggc gcc atc aac 1008 Thr Asn Cys Ser Ala Gly Glu His Asn Pro Phe Lys Gly Ala Ile Asn 325 330 335	
	ttt gac aac att ggc tat gcc tgg atc gcc atc ttc cag gtc atc acg 1056 Phe Asp Asn Ile Gly Tyr Ala Trp Ile Ala Ile Phe Gln Val Ile Thr 340 345 350	
60	ctg gag ggc tgg gtc gac atc atg tac ttt gtg atg gat gct cat tcc 1104 Leu Glu Gly Trp Val Asp Ile Met Tyr Phe Val Met Asp Ala His Ser 355 360 365	
	ttc tac aat ttc atc tac ttc atc ctc ctc atc atc gtg ggc tcc ttc 1152 Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile Val Gly Ser Phe 370 375 380	



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	Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr Gln Phe Ser Glu	
	385 390 395 400	
5	acc aag cag cgg gaa agc cag ctg atg cgg gag cag cgt ggg cgg ttc	1248
	Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln Arg Val Arg Phe	
	405 410 415	
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	Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala	
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	Arg Arg Leu Ala Gln Val Ser Arg Ala Ala Gly Val Arg Val Gly Leu	
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	Ser Cys Ser Arg Ser His Arg Arg Leu Ser Val His His Leu Val His	
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	Ile Ser Val Trp Glu Ile Val Gly Gln Gln Gly Gly Gly Leu Ser Val	
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50 ggg ccg ggg tca gca gaa aag gac ccg ggc agc gcg gac tcc gag gcg 144  
 Gly Pro Gly Ser Ala Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala  
 35 40 45

55 gag ggg ctg ccg tac ccg gcg ctg gcc ccg gtg gtt ttc ttc tac ttg 192  
 Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu  
 50 55 60

60 agc cag gac agc cgc ccg cgg agc tgg tgt ctc cgc acg gtc tgt aac 240  
 Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn  
 65 70 75 80

ccc tgg ttt gag cgc atc agc atg ttg gtc atc ctt ctc aac tgc gtg 288  
 Pro Trp Phe Glu Arg Ile Ser Met Leu Val Ile Leu Leu Asn Cys Val  
 85 90 95

acc ctg ggc atg ttc cgg cca tgc gag gac atc gcc tgt gac tcc cag 336  
 Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln  
 100 105 110



	cgc	ggc	egg	atc	ctg	cag	gcc	ttt	gat	gac	ttc	atc	ttt	ggc	ttc	ttt	384
	Arg	Cys	Arg	Ile	Leu	Gln	Ala	Phe	Asp	Asp	Phe	Ile	Phe	Ala	Phe	Phe	
			115					120					125				
5	gcc	gtg	gag	atg	gtg	gtg	aag	atg	gtg	gcc	ttg	ggc	atc	ttt	ggg	aaa	432
	Ala	Val	Glu	Met	Val	Val	Lys	Met	Val	Ala	Leu	Gly	Ile	Phe	Gly	Lys	
		130					135					140					
10	aag	tgt	tac	ctg	gga	gac	act	tgg	aac	egg	ctt	gac	ttt	ttc	atc	gtc	480
	Lys	Cys	Tyr	Leu	Gly	Asp	Thr	Trp	Asn	Arg	Leu	Asp	Phe	Phe	Ile	Val	
	145					150					155					160	
15	atc	gca	ggg	atg	ctg	gag	tac	tgg	ctg	gac	ctg	cag	aac	gtc	agc	ttc	528
	Ile	Ala	Gly	Met	Leu	Glu	Tyr	Ser	Leu	Asp	Leu	Gln	Asn	Val	Ser	Phe	
					165					170					175		
20	tca	gct	gtc	agg	aca	gtc	cgt	gtg	ctg	cga	ccg	ctc	agg	gcc	att	aac	576
	Ser	Ala	Val	Arg	Thr	Val	Arg	Val	Leu	Arg	Pro	Leu	Arg	Ala	Ile	Asn	
				180					185					190			
25	egg	gtg	ccc	agc	atg	cgc	atc	ctt	gtc	acg	ttg	ctg	ctg	gat	acg	ctg	624
	Arg	Val	Pro	Ser	Met	Arg	Ile	Leu	Val	Thr	Leu	Leu	Leu	Asp	Thr	Leu	
			195					200					205				
30	ccc	atg	ctg	ggc	aac	gtc	ctg	ctg	ctc	tgc	ttc	ttc	gtc	ttc	ttc	atc	672
	Pro	Met	Leu	Gly	Asn	Val	Leu	Leu	Leu	Cys	Phe	Phe	Val	Phe	Phe	Ile	
		210					215					220					
35	ttc	ggc	atc	gtc	ggc	gtc	cag	ctg	tgg	gca	ggg	ctg	ctt	cgg	aac	cga	720
	Phe	Gly	Ile	Val	Gly	Val	Gln	Leu	Trp	Ala	Gly	Leu	Leu	Arg	Asn	Arg	
	225					230					235					240	
40	tgc	ttc	cta	cct	gag	aat	ttc	agc	ctc	ccc	ctg	agc	gtg	gac	ctg	gag	768
	Cys	Phe	Leu	Pro	Glu	Asn	Phe	Ser	Leu	Pro	Leu	Ser	Val	Asp	Leu	Glu	
					245					250					255		
45	cgc	tat	tac	cag	aca	gag	aac	gag	gat	gag	agc	ccc	ttc	atc	tgc	tcc	816
	Arg	Tyr	Tyr	Gln	Thr	Glu	Asn	Glu	Asp	Glu	Ser	Pro	Phe	Ile	Cys	Ser	
				260					265					270			
50	cag	cca	cgc	gag	aac	ggc	atg	cgg	tcc	tgc	aga	agc	gtg	ccc	acg	ctg	864
	Gln	Pro	Arg	Glu	Asn	Gly	Met	Arg	Ser	Cys	Arg	Ser	Val	Pro	Thr	Leu	
			275					280					285				
55	cgc	ggg	gac	ggg	ggc	ggt	ggc	cca	cct	tgc	ggt	ctg	gac	tat	gag	gcc	912
	Arg	Gly	Asp	Gly	Gly	Gly	Gly	Pro	Pro	Cys	Gly	Leu	Asp	Tyr	Glu	Ala	
		290					295					300					
60	tac	aac	agc	tcc	agc	aac	acc	acc	tgt	gtc	aac	tgg	aac	cag	tac	tac	960
	Tyr	Asn	Ser	Ser	Ser	Asn	Thr	Thr	Cys	Val	Asn	Trp	Asn	Gln	Tyr	Tyr	
	305					310					315					320	
65	acc	aac	tgc	tca	gcg	ggg	gag	cac	aac	ccc	ttc	aag	ggc	gcc	atc	aac	1008
	Thr	Asn	Cys	Ser	Ala	Gly	Glu	His	Asn	Pro	Phe	Lys	Gly	Ala	Ile	Asn	
					325					330					335		
70	ttt	gac	aac	att	ggc	tat	gcc	tgg	atc	gcc	atc	ttc	cag	gtc	atc	acg	1056
	Phe	Asp	Asn	Ile	Gly	Tyr	Ala	Trp	Ile	Ala	Ile	Phe	Gln	Val	Ile	Thr	
				340				345						350			
75	ctg	gag	ggc	tgg	gtc	gac	atc	atg	tac	ttt	gtg	atg	gat	gct	cat	tcc	1104
	Leu	Glu	Gly	Trp	Val	Asp	Ile	Met	Tyr	Phe	Val	Met	Asp	Ala	His	Ser	
			355					360					365				

	ttc tac aat ttc atc tac ttc atc ctc ctc atc atc gtc ggc ttc ttc	1152
	Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile Val Gly Ser Phe	
	370 375 380	
5	ttc atg atc aac ctg tgc ctg gtc gtc att gcc acg cag ttc tca gag	1200
	Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr Gln Phe Ser Glu	
	385 390 395 400	
10	acc aag cag cgg gaa agc cag ctg atg cgg gag cag cgt gtc cgg ttc	1248
	Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln Arg Val Arg Phe	
	405 410 415	
15	ctg tcc aac gcc agc acc ctg gct agc ttc tct gag ccc ggc agc tgc	1296
	Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu Pro Gly Ser Cys	
	420 425 430	
20	tat gag gag ctg ctc aag tac ctg gtc tac atc ctt cgt aag gca gcc	1344
	Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala	
	435 440 445	
	cgc agg ctg gct cag gtc tct cgg gca gca ggt gtc cgg gtt ggg ctg	1392
	Arg Arg Leu Ala Gln Val Ser Arg Ala Ala Gly Val Arg Val Gly Leu	
	450 455 460	
25	ctc agc agc cca gca ccc ctc ggg ggc cag gag acc cag ccc agc agc	1440
	Leu Ser Ser Pro Ala Pro Leu Gly Gly Gln Glu Thr Gln Pro Ser Ser	
	465 470 475 480	
30	agc tgc tct cgc tcc cac cgc cgc cta tcc gtc cac cac ctg gtc cac	1488
	Ser Cys Ser Arg Ser His Arg Arg Leu Ser Val His His Leu Val His	
	485 490 495	
35	cac cac cac cac cat cac cac cac tac cac ctg ggc aat ggg acg ctc	1536
	His His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu	
	500 505 510	
40	agg gcc ccc cgg gcc agc ccg gag atc cag gac agg gat gcc aat ggg	1584
	Arg Ala Pro Arg Ala Ser Pro Glu Ile Gln Asp Arg Asp Ala Asn Gly	
	515 520 525	
	tcc cgc cgg ctc atg ctg cca cca ccc tgc acg cct gcc ctc tcc ggg	1632
	Ser Arg Arg Leu Met Leu Pro Pro Pro Ser Thr Pro Ala Leu Ser Gly	
	530 535 540	
45	gcc ccc cct ggt ggc gca gag tct gtc cac agc ttc tac cat gcc gac	1680
	Ala Pro Pro Gly Gly Ala Glu Ser Val His Ser Phe Tyr His Ala Asp	
	545 550 555 560	
50	tgc cac tta gag cca gtc cgc tgc cag ggc ccc cct ccc agg tcc cca	1728
	Cys His Leu Glu Pro Val Arg Cys Gln Ala Pro Pro Pro Arg Ser Pro	
	565 570 575	
55	tct gag gca tcc ggc agg act gtc ggc agc ggg aag gtc tat ccc acc	1776
	Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys Val Tyr Pro Thr	
	580 585 590	
60	gtg cac acc agc cct cca ccg gag acg ctg aag gag aag gca cta gta	1824
	Val His Thr Ser Pro Pro Pro Glu Thr Leu Lys Glu Lys Ala Leu Val	
	595 600 605	
	gag gtc gct gcc agc tct ggg ccc cca acc ctc acc agc ctc aac atc	1872
	Glu Val Ala Ala Ser Ser Gly Pro Pro Thr Leu Thr Ser Leu Asn Ile	
	610 615 620	

	cca	ccc	ggg	ccc	tac	agc	ccc	atg	cac	aag	ctg	ctg	gag	aca	cag	agt	1920
	Pro	Pro	Gly	Pro	Tyr	Ser	Ser	Met	His	Lys	Leu	Leu	Glu	Thr	Gln	Ser	
	625					630					635					640	
5	aca	ggt	gcc	tgc	caa	agc	tct	tgc	aag	atc	ccc	agc	ccc	tgc	atg	aaa	1968
	Thr	Gly	Ala	Cys	Gln	Ser	Ser	Cys	Lys	Ile	Ser	Ser	Pro	Cys	Leu	Lys	
					645					650					655		
10	gca	gac	agt	gga	gcc	tgt	ggt	cca	gac	agc	tgc	ccc	tac	tgt	gcc	cgg	2016
	Ala	Asp	Ser	Gly	Ala	Cys	Gly	Pro	Asp	Ser	Cys	Pro	Tyr	Cys	Ala	Arg	
				660					665					670			
15	gcc	ggg	gca	ggg	gag	gtg	gag	ctc	gcc	gac	cgt	gaa	atg	ccc	gac	tca	2064
	Ala	Gly	Ala	Gly	Glu	Val	Glu	Leu	Ala	Asp	Arg	Glu	Met	Pro	Asp	Ser	
				675				680					685				
20	gac	agc	gag	gca	gtt	tat	gag	ttc	aca	cag	gat	gcc	cag	cac	agc	gac	2112
	Asp	Ser	Glu	Ala	Val	Tyr	Glu	Phe	Thr	Gln	Asp	Ala	Gln	His	Ser	Asp	
		690					695					700					
	ctc	cgg	gac	ccc	cac	agc	cgg	cgg	caa	cgg	agc	ctg	ggc	cca	gat	gca	2160
	Leu	Arg	Asp	Pro	His	Ser	Arg	Arg	Gln	Arg	Ser	Leu	Gly	Pro	Asp	Ala	
	705					710					715					720	
25	gag	ccc	agc	tct	gtg	ctg	gcc	ttc	tgg	agg	cta	atc	tgt	gac	acc	ttc	2208
	Glu	Pro	Ser	Ser	Val	Leu	Ala	Phe	Trp	Arg	Leu	Ile	Cys	Asp	Thr	Phe	
					725					730					735		
30	cga	aag	att	gtg	gac	agc	aag	tac	ttt	ggc	cgg	gga	atc	atg	atc	gcc	2256
	Arg	Lys	Ile	Val	Asp	Ser	Lys	Tyr	Phe	Gly	Arg	Gly	Ile	Met	Ile	Ala	
				740					745					750			
35	atc	ctg	gtc	aac	aca	ctc	agc	atg	ggc	atc	gaa	tac	cac	gag	cag	ccc	2304
	Ile	Leu	Val	Asn	Thr	Leu	Ser	Met	Gly	Ile	Glu	Tyr	His	Glu	Gln	Pro	
			755					760					765				
40	gag	gag	ctt	acc	aac	gcc	cta	gaa	atc	agc	aac	atc	gtc	ttc	acc	agc	2352
	Glu	Glu	Leu	Thr	Asn	Ala	Leu	Glu	Ile	Ser	Asn	Ile	Val	Phe	Thr	Ser	
		770					775					780					
	ctc	ttt	gcc	ctg	gag	atg	ctg	ctg	aag	ctg	ctt	gtg	tat	ggt	ccc	ttt	2400
	Leu	Phe	Ala	Leu	Glu	Met	Leu	Leu	Lys	Leu	Leu	Val	Tyr	Gly	Pro	Phe	
	785					790					795					800	
45	ggc	tac	atc	aag	aat	ccc	tac	aac	atc	ttc	gat	ggt	gtc	att	gtg	gtc	2448
	Gly	Tyr	Ile	Lys	Asn	Pro	Tyr	Asn	Ile	Phe	Asp	Gly	Val	Ile	Val	Val	
					805					810					815		
50	atc	agc	gtg	tgg	gag	atc	gtg	ggc	cag	cag	ggg	ggc	ggc	ctg	tgg	gtg	2496
	Ile	Ser	Val	Trp	Glu	Ile	Val	Gly	Gln	Gln	Gly	Gly	Gly	Leu	Ser	Val	
				820					825					830			
55	ctg	cgg	acc	ttc	cgc	ctg	atg	cgt	gtg	ctg	aag	ctg	gtg	cgc	ttc	ctg	2544
	Leu	Arg	Thr	Phe	Arg	Leu	Met	Arg	Val	Leu	Lys	Leu	Val	Arg	Phe	Leu	
			835					840					845				
60	ccg	gcg	ctg	cag	cgg	cag	ctg	gtg	gtg	ctc	atg	aag	acc	atg	gac	aac	2592
	Pro	Ala	Leu	Gln	Arg	Gln	Leu	Val	Val	Leu	Met	Lys	Thr	Met	Asp	Asn	
		850					855					860					
	gtg	gcc	acc	ttc	tgc	atg	ctg	ctt	atg	ctc	ttc	atc	ttc	atc	ttc	agc	2640
	Val	Ala	Thr	Phe	Cys	Met	Leu	Leu	Met	Leu	Phe	Ile	Phe	Ile	Phe	Ser	
	865					870					875					880	

	atc	cag	ggc	arg	cat	ctc	ttc	ggc	tgc	aag	ttt	gac	tct	gag	egg	gat	2633
	Ile	Leu	Gly	Met	His	Leu	Phe	Gly	Cys	Lys	Phe	Ala	Ser	Glu	Arg	Asp	
					285					390					395		
5	ggg	gac	acc	ctg	cca	gac	cgg	aag	aat	ttt	gac	tcc	ttg	ctc	egg	gcc	2736
	Gly	Asp	Thr	Leu	Pro	Asp	Arg	Lys	Asn	Phe	Asp	Ser	Leu	Leu	Trp	Ala	
				900				905					910				
10	atc	gtc	act	gtc	ttt	cag	atc	ctg	acc	cag	gag	gac	ttg	aac	aaa	gtc	2784
	Ile	Val	Thr	Val	Phe	Gln	Ile	Leu	Thr	Gln	Glu	Asp	Trp	Asn	Lys	Val	
				915				920					925				
15	ctc	tac	aat	ggc	atg	gcc	tcc	acg	tgc	tcc	ttg	gcg	gcc	cct	tat	ttc	2832
	Leu	Tyr	Asn	Gly	Met	Ala	Ser	Thr	Ser	Ser	Trp	Ala	Ala	Leu	Tyr	Phe	
		930					935					940					
20	att	gcc	ctc	atg	acc	ttc	ggc	aac	tac	gtg	ctc	ttc	aat	ttg	ctg	gtc	2880
	Ile	Ala	Leu	Met	Thr	Phe	Gly	Asn	Tyr	Val	Leu	Phe	Asn	Leu	Leu	Val	
		945				950					955					960	
25	gcc	att	ctg	gtg	gag	ggc	ttc	cag	gcg	gag	gga	gat	gcc	aac	aag	tcc	2928
	Ala	Ile	Leu	Val	Glu	Gly	Phe	Gln	Ala	Glu	Gly	Asp	Ala	Asn	Lys	Ser	
					965					970					975		
30	gaa	tca	gag	ccc	gat	ttc	ttc	tca	ccc	agc	ctg	gat	ggc	gat	ggg	gac	2976
	Glu	Ser	Glu	Pro	Asp	Phe	Phe	Ser	Pro	Ser	Leu	Asp	Gly	Asp	Gly	Asp	
				980					985					990			
35	agg	aag	aag	tgc	ttg	gcc	ttg	gtg	tcc	ctg	gga	gag	cac	ccg	gag	ctg	3024
	Arg	Lys	Lys	Cys	Leu	Ala	Leu	Val	Ser	Leu	Gly	Glu	His	Pro	Glu	Leu	
			995				1000						1005				
40	cgg	aag	agc	ctg	ctg	ccg	cct	ctc	atc	atc	cac	acg	gcc	gcc	aca	ccc	3072
	Arg	Lys	Ser	Leu	Leu	Pro	Pro	Leu	Ile	Ile	His	Thr	Ala	Ala	Thr	Pro	
		1010				1015					1020						
45	atg	tgc	ctg	ccc	aag	agc	acc	agc	acg	ggc	ctg	ggc	gag	gcg	ctg	ggc	3120
	Met	Ser	Leu	Pro	Lys	Ser	Thr	Ser	Thr	Gly	Leu	Gly	Glu	Ala	Leu	Gly	
		1025			1030					1035					1040		
50	cct	gcg	tgc	cgc	cgc	acc	agc	agc	agc	ggg	tgc	gca	gag	cct	ggg	gcg	3168
	Pro	Ala	Ser	Arg	Arg	Thr	Ser	Ser	Ser	Gly	Ser	Ala	Glu	Pro	Gly	Ala	
				1045						1050				1055			
55	gcc	cac	gag	atg	aag	tca	ccg	ccc	agc	gcc	cgc	agc	tct	ccg	cac	agc	3216
	Ala	His	Glu	Met	Lys	Ser	Pro	Pro	Ser	Ala	Arg	Ser	Ser	Pro	His	Ser	
				1060				1065					1070				
60	ccc	tgg	agc	gct	gca	agc	agc	tgg	acc	agc	agg	cgc	tcc	agc	cgg	aac	3264
	Pro	Trp	Ser	Ala	Ala	Ser	Ser	Trp	Thr	Ser	Arg	Arg	Ser	Ser	Arg	Asn	
				1075				1080					1085				
65	agc	ctc	ggc	cgt	gca	ccc	agc	ctg	aag	cgg	aga	agc	cca	agt	gga	gag	3312
	Ser	Leu	Gly	Arg	Ala	Pro	Ser	Leu	Lys	Arg	Arg	Ser	Pro	Ser	Gly	Glu	
		1090				1095					1100						
70	cgg	cgg	tcc	ctg	ttg	tgc	gga	gaa	ggc	cag	gag	agc	cag	gat	gaa	gag	3360
	Arg	Arg	Ser	Leu	Leu	Ser	Gly	Glu	Gly	Gln	Glu	Ser	Gln	Asp	Glu	Glu	
		1105			1110					1115					1120		
75	gag	agc	tca	gaa	gag	gag	cgg	gcc	agc	cct	gcg	ggc	agt	gac	cat	cgc	3408
	Glu	Ser	Ser	Glu	Glu	Glu	Arg	Ala	Ser	Pro	Ala	Gly	Ser	Asp	His	Arg	
				1125				1130							1135		

	caa agg ggg tcc ctg gag cgg gag gcc aag agt tcc ttt gac ctg cca	3456
	His Arg Gly Ser Leu Glu Arg Glu Ala Lys Ser Ser Phe Asp Leu Pro	
	1140 1145 1150	
5	gac aca ctg cag gtg cca ggg ctg cat cgc act gcc agt ggc cga ggg	3504
	Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly Arg Gly	
	1155 1160 1165	
10	tct gct tct gag caa cag gac tgc aat ggc aag tct gct tca ggg cgc	3552
	Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser Gly Arg	
	1170 1175 1180	
15	ctg gcc cgg gcc ctg cgg cct gat gac ccc cca ctg gat ggg gat gac	3600
	Leu Ala Arg Ala Leu Arg Pro Asp Asp Pro Pro Leu Asp Gly Asp Asp	
	1185 1190 1195 1200	
20	gcc gat gac gag gcc aac ctg agc aaa ggg gaa cgg gtc cgc ggc tgg	3648
	Ala Asp Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Val Arg Ala Trp	
	1205 1210 1215	
	atc cga gcc cga ctg cct gcc tgc tgc ctg gag cga gac tcc tgg tca	3696
	Ile Arg Ala Arg Leu Pro Ala Cys Cys Leu Glu Arg Asp Ser Trp Ser	
	1220 1225 1230	
25	gcc tac atc ttc cct cct cag tcc agg ttc cgc ctg ctg tgt caa cgg	3744
	Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys His Arg	
	1235 1240 1245	
30	atc atc acc cac aag atg ttc gac cac gtg gtc ctt gtc atc atc ttc	3792
	Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile Ile Phe	
	1250 1255 1260	
35	ctt aac tgc atc acc atc gcc atg gag cgc ccc aaa att gac ccc cac	3840
	Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp Pro His	
	1265 1270 1275 1280	
40	agc gct gaa cgc atc ttc ctg acc ctg tcc aat tac atc ttc acc gca	3888
	Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe Thr Ala	
	1285 1290 1295	
	gtc ttt ctg gct gaa atg aca gtg aag gtg gtg gca ctg gcc tgg tgc	3936
	Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly Trp Cys	
	1300 1305 1310	
45	ttc ggg gag cag gcg tac ctg cgg agc agt tgg aac gtg ctg gac ggg	3984
	Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu Asp Gly	
	1315 1320 1325	
50	ctg ttg gtg ctg atc tcc gtc atc gac att ctg gtg tcc atg gtc tct	4032
	Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met Val Ser	
	1330 1335 1340	
55	gac agc ggc acc aag atc ctg ggc atg ctg agg gtg ctg cgg ctg ctg	4080
	Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg Leu Leu	
	1345 1350 1355 1360	
60	cgg acc ctg cgc ccg ctg agg gtg atc agc cgg gcg cag ggg ctg aag	4128
	Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Gln Gly Leu Lys	
	1365 1370 1375	
	ctg gtg gtg gag acg ctg atg tcc tca ctg aaa ccc atc gcc aac att	4176
	Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly Asn Ile	
	1380 1385 1390	

gta gtc atc tgc tgt gcc ttc ttc atc att ttc gcc atc ttg ggg gtg 4224  
 Val Val Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu Gly Val  
 1395 1400 1405

5 cag ctc ttc aaa ggg aag ttt ttc gtg tgc cag gcc gag gat acc agg 4272  
 Gln Leu Phe Lys Gly Lys Phe Phe Val Cys Gln Gly Glu Asp Thr Arg  
 1410 1415 1420

10 aac atc acc aat aaa tgc gac tgt gcc gag gcc agt tac cgg tgg gtc 4320  
 Asn Ile Thr Asn Lys Ser Asp Cys Ala Glu Ala Ser Tyr Arg Trp Val  
 1425 1430 1435 1440

15 cgg cac aag tac aac ttt gac aac ctt gcc cag gcc ctg atg tcc ctg 4368  
 Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met Ser Leu  
 1445 1450 1455

20 ttc gtt ttg gcc tcc aag gat ggt tgg gtg gac atc atg tac gat ggg 4416  
 Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr Asp Gly  
 1460 1465 1470

ctg gat gct gtg gcc gtg gac cag cag ccc atc atg aac cac aac ccc 4464  
 Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His Asn Pro  
 1475 1480 1485

25 tgg atg ctg ctg tac ttc atc tgc ttc ctg ctc att gtg gcc ttc ttt 4512  
 Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala Phe Phe  
 1490 1495 1500

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 Val Leu Asn Met Phe Val Gly Val Val Val Glu Asn Phe His Lys Cys  
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	Pro Gly Ile Cys Leu Arg Arg Arg Ala Pro Ser Ser Asp Ser Lys Asp	
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	Arg Ser Phe Thr Gln Leu Asn Asp Leu Ser Gly Ala Gly Gly Arg Gln	
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	Gly Pro Gly Ser Thr Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala	
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	Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu	
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	Pro Trp Phe Glu Arg Val Ser Met Leu Val Ile Leu Leu Asn Cys Val	
	85 90 95	
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	Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln	
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10	acc agg aac atc act aac aaa tcc gac tgc gct gag gcc agg tac cga Thr Arg Asn Ile Thr Asn Lys Ser Asp Cys Ala Glu Ala Ser Tyr Arg 1425 1430 1435 1440			4320
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25	gat ggg ctg gat gct gtg ggt gtg gat cag cag ccc atc atg aac cac Asp Gly Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His 1475 1480 1485			4464
30	aac ccc tgg atg ctg cta tac ttc atc tcc ttc ctc ctc atc gtg gcc Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala 1490 1495 1500			4512
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25	ggc gtg gag ctc ttt gga gac ctg gag tgt gat gag aca cac cct tgt Gly Val Glu Leu Phe Gly Asp Leu Glu Cys Asp Glu Thr His Pro Cys 1730 1735 1740	5232		
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70	aag cct ggg gct cca cac acc act gcc cac att gga gca gcc tgc ggc Lys Pro Gly Ala Pro His Thr Thr Ala His Ile Gly Ala Ala Ser Gly 1875 1880 1885	5664		
75	ttc tcc ctt gag cac ccc acg atg gta ccc cac ccc gag gag gtg cca Phe Ser Leu Glu His Pro Thr Met Val Pro His Pro Glu Glu Val Pro 1890 1895 1900	5712		
80	gtc ccc cta gga cca gac ctg ctg act gtg agg aag tct ggt gtc agc Val Pro Leu Gly Pro Asp Leu Leu Thr Val Arg Lys Ser Gly Val Ser 1905 1910 1915	5760		



	1905	1910	1915	1920	
5	cgg acg cac tct ctg ccc aat gac agc tac atg tgc cgc aat ggg agc Arg Thr His Ser Leu Pro Asn Asp Ser Tyr Met Cys Arg Asn Gly Ser	1925	1930	1935	5805
10	act gct gag aga tcc cta gga cac agg ggc tgg ggg ctg ccc aaa gcc Thr Ala Glu Arg Ser Leu Gly His Arg Gly Trp Gly Leu Pro Lys Ala	1940	1945	1950	5856
15	cag tca ggc tcc atc ttg tcc gtt cac tcc caa cca gca gac acc agc Gln Ser Gly Ser Ile Leu Ser Val His Ser Gln Pro Ala Asp Thr Ser	1955	1960	1965	5904
20	tgc atc cta cag ctt ccc aaa gat gtg cac tat ctg ctg cag cct cat Cys Ile Leu Gln Leu Pro Lys Asp Val His Tyr Leu Leu Gln Pro His	1970	1975	1980	5952
25	ggg gct ccc acc tgg ggc gcc atc cct aaa cta ccc cca cct ggc cgc Gly Ala Pro Thr Trp Gly Ala Ile Pro Lys Leu Pro Pro Pro Gly Arg	1985	1990	1995	6000
30	tcc cct ctg gct cag agg cct ctg agg cgc cag gca gca ata agg act Ser Pro Leu Ala Gln Arg Pro Leu Arg Arg Gln Ala Ala Ile Arg Thr	2005	2010	2015	6048
35	gac tcc ctg gat gtg cag ggc ctg ggt agc cgg gaa gac ctg ttg tca Asp Ser Leu Asp Val Gln Gly Leu Gly Ser Arg Glu Asp Leu Leu Ser	2020	2025	2030	6096
40	gag gtg agt ggg ccc tcc tgc cct ctg acc cgg tcc tca tcc ttc tgg Glu Val Ser Gly Pro Ser Cys Pro Leu Thr Arg Ser Ser Ser Phe Trp	2035	2040	2045	6144
45	ggc ggg tgc agc atc cag gtg cag cag cgt tcc ggc atc cag agc aaa Gly Gly Ser Ser Ile Gln Val Gln Gln Arg Ser Gly Ile Gln Ser Lys	2050	2055	2060	6192
50	gtc tcc aag cac atc cgc ctg cca gcc cct tgc cca ggc ctg gaa ccc Val Ser Lys His Ile Arg Leu Pro Ala Pro Cys Pro Gly Leu Glu Pro	2065	2070	2075	6240
55	agc tgg gcc aag gac cct cca gag acc aga agc agc tta gag ctg gac Ser Trp Ala Lys Asp Pro Pro Glu Thr Arg Ser Ser Leu Glu Leu Asp	2085	2090	2095	6288
60	acg gag ctg agc tgg att tca gga gac ctg ctt ccc agc agc cag gaa Thr Glu Leu Ser Trp Ile Ser Gly Asp Leu Leu Pro Ser Ser Gln Glu	2100	2105	2110	6336
65	gaa ccc ctg ttc cca cgg gac ctg aag aag tgc tac agt gta gag acc Glu Pro Leu Phe Pro Arg Asp Leu Lys Lys Cys Tyr Ser Val Glu Thr	2115	2120	2125	6384
70	cag agc tgc agg cgc agg cct ggg ttc tgg cta gat gaa cag cgg aga Gln Ser Cys Arg Arg Arg Pro Gly Phe Trp Leu Asp Glu Gln Arg Arg	2130	2135	2140	6432
75	cac tcc att gct gtc agc tgt ctg gac agc ggc tcc caa ccc cgc cta His Ser Ile Ala Val Ser Cys Leu Asp Ser Gly Ser Gln Pro Arg Leu	2145	2150	2155	6480
80	tgt cca agc ccc tca agc ctg ggg ggc caa cct ctt ggg ggt cct ggg Cys Pro Ser Pro Ser Ser Leu Gly Gly Gln Pro Leu Gly Gly Pro Gly				6528

	2165	2170	2175	
5	agg cgg cct aag aaa aaa ctc agc cca ccc agt atc tct ata gac ccc Ser Arg Pro Lys Lys Lys Leu Ser Pro Pro Ser Ile Ser Ile Asp Pro 2180 2185 2190	6576		
10	ccg gag agc cag ggc tct cgg ccc cca tgc agt cct ggt gtc tgc ctc Pro Glu Ser Gln Gly Ser Arg Pro Pro Cys Ser Pro Gly Val Cys Leu 2195 2200 2205	6624		
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20	ccc ctt gac agc acg gct gcc tca ccc tcc cca aag aaa gac acg ctg Pro Leu Asp Ser Thr Ala Ala Ser Pro Ser Pro Lys Lys Asp Thr Leu 2225 2230 2235 2240	6720		
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45	ggg ccg ggg tcg acg gaa aag gac ccg ggc agc gcg gac tcc gag gcg Gly Pro Gly Ser Thr Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala 35 40 45	144		
50	gag ggg ctg ccg tac ccg gcg cta gcc ccg gtg gtt ttc ttc tac ttg Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu 50 55 60	192		
55	agc cag gac agc cgc ccg ccg agc tgg tgt ctc cgc acg gtc tgt aac Ser Gln Asp Ser Arg Pro Arg Ser Trp Cys Leu Arg Thr Val Cys Asn 65 70 75 80	240		
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65	act ctg ggt atg ttc agg ccg tgt gag gac att gcc tgt gac tcc cag Thr Leu Gly Met Phe Arg Pro Cys Glu Asp Ile Ala Cys Asp Ser Gln 100 105 110	336		
70	cgc tgc ccg atc ctg cag gcc ttc gat gac ttc atc ttt gcc ttc ttc Arg Cys Arg Ile Leu Gln Ala Phe Asp Asp Phe Ile Phe Ala Phe Phe 115 120 125	384		

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	Lys	Cys	Tyr	Leu	Gly	Asp	Thr	Trp	Asn	Arg	Leu	Asp	Phe	Phe	Ile	Val	
	145					150					155					160	
15	att	gca	ggg	atg	ctg	gag	tat	tgg	ctg	gac	ctg	cag	aac	gtc	agc	ttc	528
	Ile	Ala	Gly	Met	Leu	Glu	Tyr	Ser	Leu	Asp	Leu	Gln	Asn	Val	Ser	Phe	
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	Ser	Ala	Val	Arg	Thr	Val	Arg	Val	Leu	Arg	Pro	Leu	Arg	Ala	Ile	Asn	
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	Arg	Val	Pro	Ser	Met	Arg	Ile	Leu	Val	Thr	Leu	Leu	Leu	Asp	Thr	Leu	
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	Pro	Met	Leu	Gly	Asn	Val	Leu	Leu	Leu	Cys	Phe	Phe	Val	Phe	Phe	Ile	
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	Cys	Phe	Leu	Pro	Glu	Asn	Phe	Ser	Leu	Pro	Leu	Ser	Val	Asp	Leu	Glu	
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	Pro	Tyr	Tyr	Gln	Thr	Glu	Asn	Glu	Asp	Glu	Ser	Pro	Phe	Ile	Cys	Ser	
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	Arg	Gly	Glu	Gly	Gly	Gly	Gly	Pro	Pro	Cys	Ser	Leu	Asp	Tyr	Glu	Thr	
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60	tat	aac	agt	tcc	agc	aac	acc	acc	tgt	gtc	aac	tgg	aac	cag	tac	tat	960
	Tyr	Asn	Ser	Ser	Ser	Asn	Thr	Thr	Cys	Val	Asn	Trp	Asn	Gln	Tyr	Tyr	
	305					310					315					320	
65	acc	aac	tgc	tct	gcg	ggc	gag	cac	aac	ccc	ttc	aaa	ggc	gcc	atc	aac	1008
	Thr	Asn	Cys	Ser	Ala	Gly	Glu	His	Asn	Pro	Phe	Lys	Gly	Ala	Ile	Asn	
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70	ttt	gac	aac	att	ggc	tat	gcc	tgg	atc	gcc	atc	ttc	cag	gtc	atc	aca	1056
	Phe	Asp	Asn	Ile	Gly	Tyr	Ala	Trp	Ile	Ala	Ile	Phe	Gln	Val	Ile	Thr	
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	Leu	Glu	Gly	Trp	Val	Asp	Ile	Met	Tyr	Phe	Val	Met	Asp	Ala	His	Ser	
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	Phe	Tyr	Asn	Phe	Ile	Tyr	Phe	Ile	Leu	Leu	Ile	Ile	Val	Gly	Ser	Phe	
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	Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu Pro Gly Ser Cys	
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	Arg Arg Leu Ala Gln Val Ser Arg Ala Ile Gly Val Arg Ala Gly Leu	
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	Leu Ser Ser Pro Val Ala Arg Ser Gly Gln Glu Pro Gln Pro Ser Gly	
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	Glu Val Ala Pro Ser Pro Gly Pro Pro Thr Leu Thr Ser Phe Asn Ile	
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	Phe Arg Lys Ile Val Asp Ser Lys Tyr Phe Gly Arg Gly Ile Met Ile	
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	755 760 765	
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	Pro Glu Glu Leu Thr Asn Ala Leu Glu Ile Ser Asn Ile Val Phe Thr	
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	Ser Leu Phe Ala Leu Glu Met Leu Leu Lys Leu Leu Val Tyr Gly Pro	
	785 790 795 800	
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	Phe Gly Tyr Ile Lys Asn Pro Tyr Asn Ile Phe Asp Gly Val Ile Val	
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	Leu Pro Ala Leu Gln Arg Gln Leu Val Val Leu Met Lys Thr Met Asp	
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	Asn Val Ala Thr Phe Cys Met Leu Leu Met Leu Phe Ile Phe Ile Phe	
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	Ser Ile Leu Gly Met His Leu Phe Gly Cys Lys Phe Ala Ser Glu Arg	
	885 890 895	

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	Asp Gly Asp Thr Leu Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu Trp	
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	Ala Ile Val Thr Val Phe Gln Ile Leu Thr Gln Glu Asp Trp Asn Lys	
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	Phe Ile Ala Leu Met Thr Phe Gly Asn Tyr Val Leu Phe Asn Leu Leu	
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	Leu Arg Lys Ser Leu Leu Pro Pro Leu Ile Ile His Thr Ala Ala Thr	
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	Gly Glu Arg Arg Ser Leu Leu Ser Gly Glu Gly Gln Glu Ser Gln Asp	
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	Glu Glu Glu Ser Ser Glu Glu Asp Arg Ala Ser Pro Ala Gly Ser Asp	
	1125 1130 1135	
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	1140 1145 1150	

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	Trp Ser Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys	
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	Pro His Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe	
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	Thr Ala Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly	
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	Trp Cys Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu	
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 2180 2185 2190

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 Glu Gly Leu Pro Tyr Pro Ala Leu Ala Pro Val Val Phe Phe Tyr Leu  
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	Phe Gly Ile Val Gly Val Gln Leu Trp Ala Gly Leu Leu Arg Asn Arg	
	225 230 235 240	
40	tgc ttc ctc ccc gag aac ttc agc ctc ccc ctg agc gtg gac ctg gag	768
	Cys Phe Leu Pro Glu Asn Phe Ser Leu Pro Leu Ser Val Asp Leu Glu	
	245 250 255	
45	cct tat tac cag aca gag aat gag gac gag agc ccc ttc atc tgc tct	816
	Pro Tyr Tyr Gln Thr Glu Asn Glu Asp Glu Ser Pro Phe Ile Cys Ser	
	260 265 270	
50	cag cct cgg gag aat ggc atg aga tcc tgc agg agt gtg ccc aca ctg	864
	Gln Pro Arg Glu Asn Gly Met Arg Ser Cys Arg Ser Val Pro Thr Leu	
	275 280 285	
55	cgt ggg gaa ggc ggt ggt ggc cca ccc tgc agt ctg gac tat gag acc	912
	Arg Gly Glu Gly Gly Gly Gly Pro Pro Cys Ser Leu Asp Tyr Glu Thr	
	290 295 300	
60	tat aac agt tcc agc aac acc acc tgt gtc aac tgg aac cag tac tat	960
	Tyr Asn Ser Ser Ser Asn Thr Thr Cys Val Asn Trp Asn Gln Tyr Tyr	
	305 310 315 320	
65	acc aac tgc tct gcg ggc gag cac aac ccc ttc aaa ggc gcc atc aac	1008
	Thr Asn Cys Ser Ala Gly Glu His Asn Pro Phe Lys Gly Ala Ile Asn	
	325 330 335	
70	ttt gac aac att ggc tat gcc tgg atc gcc atc ttc cag gtc atc aca	1056
	Phe Asp Asn Ile Gly Tyr Ala Trp Ile Ala Ile Phe Gln Val Ile Thr	
	340 345 350	
75	ctg gag ggc tgg gtc gac atc atg tac ttc gta atg gac gct cac tcc	1104
	Leu Glu Gly Trp Val Asp Ile Met Tyr Phe Val Met Asp Ala His Ser	
	355 360 365	

	ttc tac aac ttc atc tac ttc att ctt ctc atc atc gtg ggc tcc ttc	1152
	Phe Tyr Asn Phe Ile Tyr Phe Ile Leu Leu Ile Ile Val Gly Ser Phe	
	370 375 380	
5	ttc atg atc aac ctg tgc ctg gtg gtg att gcc acg cag ttc tcc gag	1200
	Phe Met Ile Asn Leu Cys Leu Val Val Ile Ala Thr Gln Phe Ser Glu	
	385 390 395 400	
10	acc aaa cag cgg gag agt cag ctg atg cgg gag cag cgt gta cga ttc	1248
	Thr Lys Gln Arg Glu Ser Gln Leu Met Arg Glu Gln Arg Val Arg Phe	
	405 410 415	
15	ctg tcc aat gct agc acc ctg gca agc ttc tct gag cca ggc agc tgc	1296
	Leu Ser Asn Ala Ser Thr Leu Ala Ser Phe Ser Glu Pro Gly Ser Cys	
	420 425 430	
20	tat gag gag cta ctc aag tac ctg gtg tac atc ctc cga aaa gca gcc	1344
	Tyr Glu Glu Leu Leu Lys Tyr Leu Val Tyr Ile Leu Arg Lys Ala Ala	
	435 440 445	
25	cga agg ctg gcc cag gtc tct agg gct ata ggc gtg cgg gct ggg ctg	1392
	Arg Arg Leu Ala Gln Val Ser Arg Ala Ile Gly Val Arg Ala Gly Leu	
	450 455 460	
30	ctc agc agc cca gtg gcc cgt agt ggg cag gag ccc cag ccc agt ggc	1440
	Leu Ser Ser Pro Val Ala Arg Ser Gly Gln Glu Pro Gln Pro Ser Gly	
	465 470 475 480	
35	agc tgc act cgc tca cac cgt cgt ctg tct gtc cac cac ctg gtc cac	1488
	Ser Cys Thr Arg Ser His Arg Arg Leu Ser Val His His Leu Val His	
	485 490 495	
40	cac cat cac cac cac cat cac cac tac cac ctg ggt aat ggg acg ctc	1536
	His His His His His His His His Tyr His Leu Gly Asn Gly Thr Leu	
	500 505 510	
45	aga gtt ccc cgg gcc agc cca gag atc cag gac agg gat gcc aat ggg	1584
	Arg Val Pro Arg Ala Ser Pro Glu Ile Gln Asp Arg Asp Ala Asn Gly	
	515 520 525	
50	tct cgc cgg ctc atg cta cca cca ccc tct aca ccc act ccc tct ggg	1632
	Ser Arg Arg Leu Met Leu Pro Pro Pro Ser Thr Pro Thr Pro Ser Gly	
	530 535 540	
55	ggc cct ccg agg ggt gcg gag tct gta cac agc ttc tac cat gct gac	1680
	Gly Pro Pro Arg Gly Ala Glu Ser Val His Ser Phe Tyr His Ala Asp	
	545 550 555 560	
60	tgc cac ttg gag cca gtc cgt tgc cag gca ccc cct ccc aga tgc cca	1728
	Cys His Leu Glu Pro Val Arg Cys Gln Ala Pro Pro Pro Arg Cys Pro	
	565 570 575	
65	tcg gag gca tct ggt agg act gtg ggt agt ggg aag gtg tac ccc act	1776
	Ser Glu Ala Ser Gly Arg Thr Val Gly Ser Gly Lys Val Tyr Pro Thr	
	580 585 590	
70	gtg cat acc agc cct cca cca gag ata ctg aag gat aaa gca cta gtg	1824
	Val His Thr Ser Pro Pro Pro Glu Ile Leu Lys Asp Lys Ala Leu Val	
	595 600 605	
75	gag gtg gcc ccc agc cct ggg ccc ccc acc ctc acc agc ttc aac atc	1872
	Glu Val Ala Pro Ser Pro Gly Pro Pro Thr Leu Thr Ser Phe Asn Ile	
	610 615 620	

	cca cct ggg ccc ttc agc tcc atg cac aag ctc ctg gag aca cag agt	1920
	Pro Pro Gly Pro Phe Ser Ser Met His Lys Leu Leu Glu Thr Gln Ser	
	625 630 635 640	
5	acg gga gcc tgc cat agc tcc tgc aaa atc tcc agc cct tgc tcc aag	1968
	Thr Gly Ala Cys His Ser Ser Cys Lys Ile Ser Ser Pro Cys Ser Lys	
	645 650 655	
10	gca gac agt gga gcc tgc ggg ccg gac agt tgt ccc tac tgt gcc cgg	2016
	Ala Asp Ser Gly Ala Cys Gly Pro Asp Ser Cys Pro Tyr Cys Ala Arg	
	660 665 670	
15	aca gga gca gga gag cca gag tcc gct gac cat gtc atg cct gac tca	2064
	Thr Gly Ala Gly Glu Pro Glu Ser Ala Asp His Val Met Pro Asp Ser	
	675 680 685	
20	gac agc gag gct gtg tat gag ttc aca cag gac gct cag cac agt gac	2112
	Asp Ser Glu Ala Val Tyr Glu Phe Thr Gln Asp Ala Gln His Ser Asp	
	690 695 700	
	ctc cgg gat ccc cac agc cgg cgg cga cag cgg agc ctg ggc cca gat	2160
	Leu Arg Asp Pro His Ser Arg Arg Arg Gln Arg Ser Leu Gly Pro Asp	
	705 710 715 720	
25	gca gag cct agt tct gtg ctg gct ttc tgg agg ctg atc tgt gac aca	2208
	Ala Glu Pro Ser Ser Val Leu Ala Phe Trp Arg Leu Ile Cys Asp Thr	
	725 730 735	
30	ttc cgg aag atc gta gat agc aaa tac ttt ggc cgg gga atc atg atc	2256
	Phe Arg Lys Ile Val Asp Ser Lys Tyr Phe Gly Arg Gly Ile Met Ile	
	740 745 750	
35	gcc atc ctg gtc aat aca ctc agc atg ggc atc gag tac cac gag cag	2304
	Ala Ile Leu Val Asn Thr Leu Ser Met Gly Ile Glu Tyr His Glu Gln	
	755 760 765	
40	ccc gag gag ctc acc aac gcc ctg gaa atc agc aac atc gtc ttc acc	2352
	Pro Glu Glu Leu Thr Asn Ala Leu Glu Ile Ser Asn Ile Val Phe Thr	
	770 775 780	
	agc ctc ttc gcc ttg gag atg ctg ctg aaa ctg ctt gtc tac ggt ccc	2400
	Ser Leu Phe Ala Leu Glu Met Leu Leu Lys Leu Leu Val Tyr Gly Pro	
	785 790 795 800	
45	ttt ggc tac att aag aat ccc tac aac atc ttt gat ggt gtc att gtg	2448
	Phe Gly Tyr Ile Lys Asn Pro Tyr Asn Ile Phe Asp Gly Val Ile Val	
	805 810 815	
50	gtc atc agt gtg tgg gag att gtg ggc cag cag gga ggt ggc ctg tcg	2496
	Val Ile Ser Val Trp Glu Ile Val Gly Gln Gln Gly Gly Gly Leu Ser	
	820 825 830	
55	gtg ctg cgg acc ttc cgc ctg atg cgg gtg ctg aag ctg gtg cgc ttc	2544
	Val Leu Arg Thr Phe Arg Leu Met Arg Val Leu Lys Leu Val Arg Phe	
	835 840 845	
60	ctg ccg gcc ctg cag cgc cag ctc gtg gtg ctc atg aag acc atg gac	2592
	Leu Pro Ala Leu Gln Arg Gln Leu Val Val Leu Met Lys Thr Met Asp	
	850 855 860	
	aac gtg gcc acc ttc tgc atg ctc ctc atg ctg ttc atc ttc atc ttc	2640
	Asn Val Ala Thr Phe Cys Met Leu Leu Met Leu Phe Ile Phe Ile Phe	
	865 870 875 880	

	agc atc ctg ggc atg cat ctc ttt ggt tgc aag ttc gca tct gaa cgg	2688
	Ser Ile Leu Gly Met His Leu Phe Gly Cys Lys Phe Ala Ser Glu Arg	
	385 890 895	
5	gat ggg gac acg ttg cca gac cgg aag aat ttc gac tcc ctg ctc tgg	2736
	Asp Gly Asp Thr Leu Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu Trp	
	900 905 910	
10	gcc atc gtc act gtc ttt cag att ctg act cag gaa gac tgg aat aaa	2784
	Ala Ile Val Thr Val Phe Gln Ile Leu Thr Gln Glu Asp Trp Asn Lys	
	915 920 925	
15	gtc ctc tac aac ggc atg gcc tcc aca tcg tct tgg gct gct ctt tac	2832
	Val Leu Tyr Asn Gly Met Ala Ser Thr Ser Ser Trp Ala Ala Leu Tyr	
	930 935 940	
20	ttc atc gcc ctc atg act ttt ggc aac tat gtg ctc ttt aac ctg ctg	2880
	Phe Ile Ala Leu Met Thr Phe Gly Asn Tyr Val Leu Phe Asn Leu Leu	
	945 950 955 960	
	gtg gcc att ctt gtg gaa gga ttc cag gca gag gga gat gcc acc aag	2928
	Val Ala Ile Leu Val Glu Gly Phe Gln Ala Glu Gly Asp Ala Thr Lys	
	965 970 975	
25	tct gag tca gag cct gat ttc ttt tcg ccc agt gtg gat ggt gat ggg	2976
	Ser Glu Ser Glu Pro Asp Phe Phe Ser Pro Ser Val Asp Gly Asp Gly	
	980 985 990	
30	gac aga aag aag cgc ttg gcc ctg gtg gct ttg gga gaa cac gcg gaa	3024
	Asp Arg Lys Lys Arg Leu Ala Leu Val Ala Leu Gly Glu His Ala Glu	
	995 1000 1005	
35	cta cga aag agc ctt ttg cca ccc ctc atc atc cat acg gct gcg aca	3072
	Leu Arg Lys Ser Leu Leu Pro Pro Leu Ile Ile His Thr Ala Ala Thr	
	1010 1015 1020	
40	cca atg tca cac ccc aag agc tcc agc aca ggt gtg ggg gaa gca ctg	3120
	Pro Met Ser His Pro Lys Ser Ser Ser Thr Gly Val Gly Glu Ala Leu	
	1025 1030 1035 1040	
	ggc tct ggc tct cga cgt acc agt agc agt ggg tcc gct gag cct gga	3168
	Gly Ser Gly Ser Arg Arg Thr Ser Ser Ser Gly Ser Ala Glu Pro Gly	
	1045 1050 1055	
45	gct gcc cac cat gag atg aaa tgt ccg cca agt gcc cgc agc tcc ccg	3216
	Ala Ala His His Glu Met Lys Cys Pro Pro Ser Ala Arg Ser Ser Pro	
	1060 1065 1070	
50	cac agt ccc tgg agt gcg gca agc agc tgg acc agc agg cgc tcc agc	3264
	His Ser Pro Trp Ser Ala Ala Ser Ser Trp Thr Ser Arg Arg Ser Ser	
	1075 1080 1085	
55	agg aac agc ctg ggc cgg gcc ccc agc cta aag cgg agg agc ccg agc	3312
	Arg Asn Ser Leu Gly Arg Ala Pro Ser Leu Lys Arg Arg Ser Pro Ser	
	1090 1095 1100	
60	ggg gag cgg agg tcc ctg ctg tct gga gag ggc cag gag agt cag gat	3360
	Gly Glu Arg Arg Ser Leu Leu Ser Gly Glu Gly Gln Glu Ser Gln Asp	
	1105 1110 1115 1120	
	gag gag gaa agt tca gaa gag gac cgg gcc agc cca gca ggc agt gac	3408
	Glu Glu Glu Ser Ser Glu Glu Asp Arg Ala Ser Pro Ala Gly Ser Asp	
	1125 1130 1135	

	cat cgc cac agg ggt tcc ttg gaa cgt gag gcc aag agt tcc ttc gac His Arg His Arg Gly Ser Leu Glu Arg Glu Ala Lys Ser Ser Phe Asp 1140 1145 1150	3456
5	ctg cct gac act ctg cag gtg ccg ggg ctg cac cgc aca gcc agc ggc Leu Pro Asp Thr Leu Gln Val Pro Gly Leu His Arg Thr Ala Ser Gly 1155 1160 1165	3504
10	cgg agc tct gcc tct gag cac caa gac tgt aat ggc aag tgg gct tca Arg Ser Ser Ala Ser Glu His Gln Asp Cys Asn Gly Lys Ser Ala Ser 1170 1175 1180	3552
15	ggg cgt ttg gcc cgc acc ctg agg act gat gac ccc caa ctg gat ggg Gly Arg Leu Ala Arg Thr Leu Arg Thr Asp Asp Pro Gln Leu Asp Gly 1185 1190 1195 1200	3600
20	gat gat gac aat gat gag gga aat ctg agc aaa ggg gaa cgc ata caa Asp Asp Asp Asn Asp Glu Gly Asn Leu Ser Lys Gly Glu Arg Ile Gln 1205 1210 1215	3648
	gcc tgg gtc aga tcc cgg ctt cct gcc tgt tgc cga gag cga gat tcc Ala Trp Val Arg Ser Arg Leu Pro Ala Cys Cys Arg Glu Arg Asp Ser 1220 1225 1230	3696
25	tgg tgg gcc tat atc ttt cct cct cag tca agg ttt cgt ctc ctg tgt Trp Ser Ala Tyr Ile Phe Pro Pro Gln Ser Arg Phe Arg Leu Leu Cys 1235 1240 1245	3744
30	cac cgg atc atc acc cac aag atg ttt gac cat gtg gtc ctc gtc atc His Arg Ile Ile Thr His Lys Met Phe Asp His Val Val Leu Val Ile 1250 1255 1260	3792
35	atc ttc ctc aac tgt atc acc atc gct atg gag cgc ccc aaa att gac Ile Phe Leu Asn Cys Ile Thr Ile Ala Met Glu Arg Pro Lys Ile Asp 1265 1270 1275 1280	3840
40	ccc cac agc gct gag cgc atc ttc ctg acc ctc tcc aac tac atc ttc Pro His Ser Ala Glu Arg Ile Phe Leu Thr Leu Ser Asn Tyr Ile Phe 1285 1290 1295	3888
	acg gca gtc ttt cta gct gaa atg aca gtg aag gtg gtg gca ctg ggc Thr Ala Val Phe Leu Ala Glu Met Thr Val Lys Val Val Ala Leu Gly 1300 1305 1310	3936
45	tgg tgc ttt ggg gag cag gcc tac ctg cgc agc agc tgg aat gtg ctg Trp Cys Phe Gly Glu Gln Ala Tyr Leu Arg Ser Ser Trp Asn Val Leu 1315 1320 1325	3984
50	gac ggc ttg ctg gtg ctc atc tcc gtc atc gac atc ctg gtc tcc atg Asp Gly Leu Leu Val Leu Ile Ser Val Ile Asp Ile Leu Val Ser Met 1330 1335 1340	4032
55	gtc tcc gac agc ggc acc aag atc ctt ggc atg ctg agg gtg ctg cgg Val Ser Asp Ser Gly Thr Lys Ile Leu Gly Met Leu Arg Val Leu Arg 1345 1350 1355 1360	4080
	ctg ctg cgg acc ctg cgt cca ctc agg gtc atc agc cgg gcc cag gga Leu Leu Arg Thr Leu Arg Pro Leu Arg Val Ile Ser Arg Ala Gln Gly 1365 1370 1375	4128
60	ctg aag ctg gtg gta gag act ctg atg tca tcc ctc aaa ccc att ggc Leu Lys Leu Val Val Glu Thr Leu Met Ser Ser Leu Lys Pro Ile Gly 1380 1385 1390	4176



	aac att ggc gtc att tgc tgt gcc ttc ttc atc att ttt gga att ctc	4224
	Asn Ile Val Val Ile Cys Cys Ala Phe Phe Ile Ile Phe Gly Ile Leu	
	1395 1400 1405	
5	ggg gtg cag ctc ttc aaa ggg aag ttc ttc gtg tgt cag ggt gag gac	4272
	Gly Val Gln Leu Phe Lys Gly Lys Phe Phe Val Cys Gln Gly Glu Asp	
	1410 1415 1420	
10	acc agg aac atc act aac aaa tcc gac tgc gct gag gcc agt tac cga	4320
	Thr Arg Asn Ile Thr Asn Lys Ser Asp Cys Ala Glu Ala Ser Tyr Arg	
	1425 1430 1435 1440	
15	tgg gtc cgg cac aag tac aac ttt gac aac ctg ggc cag gct ctg atg	4368
	Trp Val Arg His Lys Tyr Asn Phe Asp Asn Leu Gly Gln Ala Leu Met	
	1445 1450 1455	
20	tcc ctg ttt gtg ctg gcc tcc aag gat ggt tgg gtt gac atc atg tac	4416
	Ser Leu Phe Val Leu Ala Ser Lys Asp Gly Trp Val Asp Ile Met Tyr	
	1460 1465 1470	
25	gat ggg ctg gat gct gtg ggt gtg gat cag cag ccc atc atg aac cac	4464
	Asp Gly Leu Asp Ala Val Gly Val Asp Gln Gln Pro Ile Met Asn His	
	1475 1480 1485	
30	aac ccc tgg atg ctg cta tac ttc atc tcc ttc ctc ctc atc gtg gcc	4512
	Asn Pro Trp Met Leu Leu Tyr Phe Ile Ser Phe Leu Leu Ile Val Ala	
	1490 1495 1500	
35	ttc ttt gtc ctg aac atg ttt gtg ggc gtg gtg gtg gag aac ttc cat	4560
	Phe Phe Val Leu Asn Met Phe Val Gly Val Val Glu Asn Phe His	
	1505 1510 1515 1520	
40	aag tgc aga cag cac cag gag gag gag gag ggc agg cgg cgt gag gag	4608
	Lys Cys Arg Gln His Gln Glu Glu Glu Glu Ala Arg Arg Arg Glu Glu	
	1525 1530 1535	
45	aag cga cta cgg agg ctg gag aaa aag aga agg agt aag gag aag cag	4656
	Lys Arg Leu Arg Arg Leu Glu Lys Lys Arg Arg Ser Lys Glu Lys Gln	
	1540 1545 1550	
50	atg gcc gat cta atg ttg gac gat gta att gct tcc ggc agc tca gcc	4704
	Met Ala Asp Leu Met Leu Asp Asp Val Ile Ala Ser Gly Ser Ser Ala	
	1555 1560 1565	
55	agc gct gcg tca gaa gcc cag tgc aag ccc tac tac tct gac tac tgc	4752
	Ser Ala Ala Ser Glu Ala Gln Cys Lys Pro Tyr Tyr Ser Asp Tyr Ser	
	1570 1575 1580	
60	aga ttc cgg ctc ctt gtc cac cac ctg tgt acc agc cac tac ctg gac	4800
	Arg Phe Arg Leu Leu Val His His Leu Cys Thr Ser His Tyr Leu Asp	
	1585 1590 1595 1600	
65	ctc ttc atc act ggt gtc atc ggg ctg aac gtg gtc act atg gcc atg	4848
	Leu Phe Ile Thr Gly Val Ile Gly Leu Asn Val Val Thr Met Ala Met	
	1605 1610 1615	
70	gaa cat tac cag cag ccc cag atc ctg gac gag gct ctg aag atc tgc	4896
	Glu His Tyr Gln Gln Pro Gln Ile Leu Asp Glu Ala Leu Lys Ile Cys	
	1620 1625 1630	
75	aat tac atc ttt acc gtc atc ttt gtc ttt gag tca gtt ttc aaa ctc	4944
	Asn Tyr Ile Phe Thr Val Ile Phe Val Phe Glu Ser Val Phe Lys Leu	
	1635 1640 1645	

	gtg gcc ttt ggc ttc cgc cgt ttc ttc cag gac agg tgg aac cag ctg Val Ala Phe Gly Phe Arg Arg Phe Phe Gln Asp Arg Trp Asn Gln Leu 1650 1655 1660	4992
5	gac ctg gct att gtg ctt ctg tcc atc atg ggc atc aca ctg gag gag Asp Leu Ala Ile Val Leu Leu Ser Ile Met Gly Ile Thr Leu Glu Glu 1665 1670 1675 1680	5040
10	att gag gtc aat ctg tgc ctg ccc atc aac ccc acc atc atc cgt atc Ile Glu Val Asn Leu Ser Leu Pro Ile Asn Pro Thr Ile Ile Arg Ile 1685 1690 1695	5088
15	atg agg gtg ctc cgc att gct cga gtt ctg aag ctg ttg aag atg gct Met Arg Val Leu Arg Ile Ala Arg Val Leu Lys Leu Leu Lys Met Ala 1700 1705 1710	5136
20	gtg ggc atg cgg gca ctg ctg ccc acg gtg atg cag gcc ctg ccc cag Val Gly Met Arg Ala Leu Leu His Thr Val Met Gln Ala Leu Pro Gln 1715 1720 1725	5184
	gtg ggg aac ctg gga ctt ctc ttc atg tta ttg ttt ttc atc ttt gca Val Gly Asn Leu Gly Leu Leu Phe Met Leu Leu Phe Phe Ile Phe Ala 1730 1735 1740	5232
25	gct ctg ggc gtg gag ctc ttt gga gac ctg gag tgt gat gag aca cac Ala Leu Gly Val Glu Leu Phe Gly Asp Leu Glu Cys Asp Glu Thr His 1745 1750 1755 1760	5280
30	cct tgt gag ggc ttg ggt cgg cat gcc acc ttt agg aac ttt ggt atg Pro Cys Glu Gly Leu Gly Arg His Ala Thr Phe Arg Asn Phe Gly Met 1765 1770 1775	5328
35	gcc ttt ctg acc ctc ttc cga gtc tcc act ggt gac aac tgg aat ggt Ala Phe Leu Thr Leu Phe Arg Val Ser Thr Gly Asp Asn Trp Asn Gly 1780 1785 1790	5376
40	att atg aag gac acc ctc cgg gac tgt gac cag gag tcc acc tgc tac Ile Met Lys Asp Thr Leu Arg Asp Cys Asp Gln Glu Ser Thr Cys Tyr 1795 1800 1805	5424
	aac act gtc atc tcc cct atc tac ttt gtg tcc ttc gtg ctg acg gcc Asn Thr Val Ile Ser Pro Ile Tyr Phe Val Ser Phe Val Leu Thr Ala 1810 1815 1820	5472
45	cag ttt gtg ctg gtc aac gtg gtc ata gct gtg ctg atg aag cac ctg Gln Phe Val Leu Val Asn Val Val Ile Ala Val Leu Met Lys His Leu 1825 1830 1835 1840	5520
50	gaa gaa agc aac aaa gag gcc aag gag gag gcc gag ctc gag gcc gag Glu Glu Ser Asn Lys Glu Ala Lys Glu Glu Ala Glu Leu Glu Ala Glu 1845 1850 1855	5568
55	ctg gag ctg gag atg aag acg ctc agc ccg cag ccc cac tcc ccg ctg Leu Glu Leu Glu Met Lys Thr Leu Ser Pro Gln Pro His Ser Pro Leu 1860 1865 1870	5616
60	ggc agc ccc ttc ctc tgg ccc ggg gtg gag ggt gtc aac agt act gac Gly Ser Pro Phe Leu Trp Pro Gly Val Glu Gly Val Asn Ser Thr Asp 1875 1880 1885	5664
	agc cct aag cct ggg gct cca cac acc act gcc cac att gga gca gcc Ser Pro Lys Pro Gly Ala Pro His Thr Thr Ala His Ile Gly Ala Ala 1890 1895 1900	5712

	tcg ggc ttc tcc ctt gag cac ccc acg atg gta ccc cac ccc gag gag	5760
	Ser Gly Phe Ser Leu Glu His Pro Thr Met Val Pro His Pro Glu Glu	
	1905 1910 1915 1920	
5	gtg cca gtc ccc cta gga cca gac ctg ctg act gtg agg aag tct ggt	5808
	Val Pro Val Pro Leu Gly Pro Asp Leu Leu Thr Val Arg Lys Ser Gly	
	1925 1930 1935	
10	gtc agc cgg acg cac tct ctg ccc aat gac agc tac atg tgc cgc aat	5856
	Val Ser Arg Thr His Ser Leu Pro Asn Asp Ser Tyr Met Cys Arg Asn	
	1940 1945 1950	
15	ggg agc act gct gag aga tcc cta gga cac agg ggc tgg ggg ctc ccc	5904
	Gly Ser Thr Ala Glu Arg Ser Leu Gly His Arg Gly Trp Gly Leu Pro	
	1955 1960 1965	
20	aaa gcc cag tca ggc tcc atc ttg tcc gtt cac tcc caa cca gca gac	5952
	Lys Ala Gln Ser Gly Ser Ile Leu Ser Val His Ser Gln Pro Ala Asp	
	1970 1975 1980	
	acc agc tgc atc cta cag ctt ccc aaa gat gtg cac tat ctg ctc cag	6000
	Thr Ser Cys Ile Leu Gln Leu Pro Lys Asp Val His Tyr Leu Leu Gln	
	1985 1990 1995 2000	
25	cct cat ggg gct ccc acc tgg ggc gcc atc cct aaa cta ccc cca cct	6048
	Pro His Gly Ala Pro Thr Trp Gly Ala Ile Pro Lys Leu Pro Pro Pro	
	2005 2010 2015	
30	ggc cgc tcc cct ctg gct cag agg cct ctc agg cgc cag gca gca ata	6096
	Gly Arg Ser Pro Leu Ala Gln Arg Pro Leu Arg Arg Gln Ala Ala Ile	
	2020 2025 2030	
35	agg act gac tcc ctg gat gtg cag ggc ctg ggt agc cgg gaa gac ctg	6144
	Arg Thr Asp Ser Leu Asp Val Gln Gly Leu Gly Ser Arg Glu Asp Leu	
	2035 2040 2045	
40	ttg tca gag gtg agt ggg ccc tcc tgc cct ctg acc cgg tcc tca tcc	6192
	Leu Ser Glu Val Ser Gly Pro Ser Cys Pro Leu Thr Arg Ser Ser Ser	
	2050 2055 2060	
	ttc tgg ggc ggg tgc agc atc cag gtg cag cag cgt tcc ggc atc cag	6240
	Phe Trp Gly Gly Ser Ser Ile Gln Val Gln Gln Arg Ser Gly Ile Gln	
	2065 2070 2075 2080	
45	agc aaa gtc tcc aag cac atc cgc ctg cca gcc cct tgc cca ggc ctg	6288
	Ser Lys Val Ser Lys His Ile Arg Leu Pro Ala Pro Cys Pro Gly Leu	
	2085 2090 2095	
50	gaa ccc agc tgg gcc aag gac cct cca gag acc aga agc agc tta gag	6336
	Glu Pro Ser Trp Ala Lys Asp Pro Pro Glu Thr Arg Ser Ser Leu Glu	
	2100 2105 2110	
55	ctg gac acg gag ctg agc tgg att tca gga gac ctc ctt ccc agc agc	6384
	Leu Asp Thr Glu Leu Ser Trp Ile Ser Gly Asp Leu Leu Pro Ser Ser	
	2115 2120 2125	
60	cag gaa gaa ccc ctg ttc cca cgg gac ctg aag aag tgc tac agt gta	6432
	Gln Glu Glu Pro Leu Phe Pro Arg Asp Leu Lys Lys Cys Tyr Ser Val	
	2130 2135 2140	
	gag acc cag agc tgc agg cgc agg cct ggg ttc tgg cta gat gaa cag	6480
	Glu Thr Gln Ser Cys Arg Arg Arg Pro Gly Phe Trp Leu Asp Glu Gln	
	2145 2150 2155 2160	

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	Gly Pro Gly Ser Thr Glu Lys Asp Pro Gly Ser Ala Asp Ser Glu Ala	
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	Pro Trp Phe Glu Arg Val Ser Met Leu Val Ile Leu Leu Asn Cys Val	
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	1475 1480 1485	
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	Leu	Arg	Arg	Gln	Ala	Ala	Ile	Arg	Thr	Asp	Ser	Leu	Asp	Val	Gln	Gly	
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	2180 2185 2190	
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	20 25 30	
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	35 40 45	
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	50 55 60	
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	65 70 75 80	
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	85 90 95	
	tgc aac cca tgg ttc gag cac gtg agc atg ctg gta atc atg ctc aac Cys Asn Pro Trp Phe Glu His Val Ser Met Leu Val Ile Met Leu Asn	336

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	ttt ttt gcg gtg gag atg gtc atc aag atg gtg gcc ttg ggg ctg ttc Phe Phe Ala Val Glu Met Val Ile Lys Met Val Ala Leu Gly Leu Phe 145 150 155 160			480
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	Val Leu Arg Thr Phe Arg Leu Leu Arg Val Leu Lys Leu Val Arg Phe							
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	Leu Pro Ala Leu Arg Arg Gln Leu Val Val Leu Val Lys Thr Met Asp							
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	Asn Val Ala Thr Phe Cys Thr Leu Leu Met Leu Phe Ile Phe Ile Phe							
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	Ser Ile Leu Gly Met His Leu Phe Gly Cys Lys Phe Ser Leu Lys Thr							
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	Asp Thr Gly Asp Thr Val Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu							
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	Trp Ala Ile Val Thr Val Phe Gln Ile Leu Thr Gln Glu Asp Trp Asn							
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	Leu Ala Val Thr Pro Asn Gly Thr Trp Arg Asp Glu Ala Ala Cys Pro							
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	Leu Pro Ser Ser Cys Ala Gln Leu Pro Arg Pro Cys Leu Pro Pro Arg							
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	Ala His His Ser Trp Met Gln Pro Pro Ala Ser Gln Thr Leu Gly Val							
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	Ala Ala Ala Ala Pro Gly Thr Arg His Trp Glu Thr Arg Ser Leu Arg							
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	1890	1895	1900	
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70	cgg ggc gcc ggg acg cga ggc gga ggg ggg ttc gag ctc gcc gtg tca Arg Gly Ala Gly Thr Arg Gly Gly Gly Gly Phe Glu Leu Gly Val Ser 35 40 45	144		
75	ccc tcc gag agc ccg gcg gcc gag cgc tgc gcg gag ctg ggt gcc gac Pro Ser Glu Ser Pro Ala Ala Glu Arg Cys Ala Glu Leu Gly Ala Asp 50 55 60	192		

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5	tac	acg	cag	ccg	cag	gcc	gag	ggg	gtg	ggc	gct	gca	cgc	aac	gcc	tgc	1003
	Tyr	Thr	Gln	Pro	Gln	Ala	Glu	Gly	Val	Gly	Ala	Ala	Arg	Asn	Ala	Cys	
					325					330					335		
10	atc	aac	tgg	aac	cag	tac	tac	aac	gtg	tgc	cgc	tcg	ggc	gac	tcc	aac	1056
	Ile	Asn	Trp	Asn	Gln	Tyr	Tyr	Asn	Val	Cys	Arg	Ser	Gly	Asp	Ser	Asn	
					340				345					350			
15	ccc	cac	aac	ggc	gcc	atc	aac	ttc	gac	aac	acc	tgc	tac	gcc	tgg	att	1104
	Pro	His	Asn	Gly	Ala	Ile	Asn	Phe	Asp	Asn	Thr	Cys	Tyr	Ala	Trp	Ile	
					355			360					365				
20	gcc	atc	ttc	cag	gtg	atc	acg	ctg	gaa	ggc	tgg	gtg	gac	atc	atg	tac	1152
	Ala	Ile	Phe	Gln	Val	Ile	Thr	Leu	Glu	Gly	Trp	Val	Asp	Ile	Met	Tyr	
					370			375				380					
25	tac	gtc	atg	gac	gcc	cac	tca	ttc	tac	aac	ttc	atc	tac	ttc	atc	ctg	1200
	Tyr	Val	Met	Asp	Ala	His	Ser	Phe	Tyr	Asn	Phe	Ile	Tyr	Phe	Ile	Leu	
					385			390			395					400	
30	ctc	atc	atc	gtg	ggc	tcc	ttc	ttc	atg	atc	aac	ctg	tgc	ctg	gtg	gtg	1248
	Leu	Ile	Ile	Val	Gly	Ser	Phe	Phe	Met	Ile	Asn	Leu	Cys	Leu	Val	Val	
					405				410					415			
35	att	gcc	acg	cag	ttc	tcg	gag	acg	aag	cag	cgg	gag	agt	cag	ctg	atg	1296
	Ile	Ala	Thr	Gln	Phe	Ser	Glu	Thr	Lys	Gln	Arg	Glu	Ser	Gln	Leu	Met	
					420			425						430			
40	cgg	gag	cag	cgg	gca	cgc	cac	ctg	tcc	aac	gac	agc	acg	ctg	gcc	agc	1344
	Arg	Glu	Gln	Arg	Ala	Arg	His	Leu	Ser	Asn	Asp	Ser	Thr	Leu	Ala	Ser	
					435			440					445				
45	ttc	tcc	gag	cct	ggc	agc	tgc	tac	gaa	gag	ctg	ctg	aag	tac	gtg	ggc	1392
	Phe	Ser	Glu	Pro	Gly	Ser	Cys	Tyr	Glu	Glu	Leu	Leu	Lys	Tyr	Val	Gly	
					450			455				460					
50	cac	ata	ttc	cgc	aag	gtc	aag	cgg	cgc	agc	ttg	cgc	ctc	tac	gcc	cgc	1440
	His	Ile	Phe	Arg	Lys	Val	Lys	Arg	Arg	Ser	Leu	Arg	Leu	Tyr	Ala	Arg	
					465			470			475					480	
55	tgg	cag	agc	cgc	tgg	cgc	aag	aag	gtg	gac	ccc	agt	gct	gtg	caa	ggc	1488
	Trp	Gln	Ser	Arg	Trp	Arg	Lys	Lys	Val	Asp	Pro	Ser	Ala	Val	Gln	Gly	
					485				490					495			
60	cag	ggt	ccc	ggg	cac	cgc	cag	cgc	cgg	gca	ggc	agg	cac	aca	gcc	tcg	1536
	Gln	Gly	Pro	Gly	His	Arg	Gln	Arg	Arg	Ala	Gly	Arg	His	Thr	Ala	Ser	
					500				505					510			
65	gtg	cac	cac	ctg	gtc	tac	cac	cac	cat	cac	cac	cac	cac	cac	cac	tac	1584
	Val	His	His	Leu	Val	Tyr	His	His	His	His	His	His	His	His	His	Tyr	
					515			520					525				
70	cat	ttc	agc	cat	ggc	agc	ccc	cgc	agg	ccc	ggc	ccc	gag	cca	ggc	gcc	1632
	His	Phe	Ser	His	Gly	Ser	Pro	Arg	Arg	Pro	Gly	Pro	Glu	Pro	Gly	Ala	
					530			535				540					
75	tgc	gac	acc	agg	ctg	gtc	cga	gct	ggc	gcg	ccc	ccc	tcg	cca	cct	tcc	1680
	Cys	Asp	Thr	Arg	Leu	Val	Arg	Ala	Gly	Ala	Pro	Pro	Ser	Pro	Pro	Ser	
					545			550			555					560	
80	cca	ggc	cgc	gga	ccc	ccc	gac	gca	gag	tct	gtg	cac	agc	atc	tac	cat	1728
	Pro	Gly	Arg	Gly	Pro	Pro	Asp	Ala	Glu	Ser	Val	His	Ser	Ile	Tyr	His	
					565				570						575		

	gcc gac tgc cac ata gag ggg ccg cag gag agg gcc cgg gtg ggc aca	1776
5	Ala Asp Cys His Ile Glu Gly Pro Gln Glu Arg Ala Arg Val Gly Thr	
	580 585 590	
	tgc cgc agc cac tgc cgc tgc cag cct cag gct ggc cac agg gct ggg	1824
	Cys Arg Ser His Cys Arg Cys Gln Pro Gln Ala Gly His Arg Ala Gly	
	595 600 605	
10	cac cat gaa cta ccc cac gat cct gcc ctc agg ggt ggg cag cgg caa	1872
	His His Glu Leu Pro His Asp Pro Ala Leu Arg Gly Gly Gln Arg Gln	
	610 615 620	
15	agg cag cac cag ccc cgg acc caa ggg gaa gtg ggc cgg tgg acc gcc	1920
	Arg Gln His Gln Pro Arg Thr Gln Gly Glu Val Gly Arg Trp Thr Ala	
	625 630 635 640	
20	agg cac cgg ggg cac ggc ccg ttg agc ttg aac agc cct gat ccc tac	1968
	Arg His Arg Gly His Gly Pro Leu Ser Leu Asn Ser Pro Asp Pro Tyr	
	645 650 655	
25	gag aag atc ccg cat gtg gcc ggg gag cat gga ctg ggc caa gcc cct	2016
	Glu Lys Ile Pro His Val Ala Gly Glu His Gly Leu Gly Gln Ala Pro	
	660 665 670	
	ggc cat ctg tgc ggc ctc agt gtg ccc tgc ccc ctg ccc agc ccc cca	2064
	Gly His Leu Ser Gly Leu Ser Val Pro Cys Pro Leu Pro Ser Pro Pro	
	675 680 685	
30	gcg ggc aca ctg acc tgt gag ctg aag agc tgc ccg tac tgc acc cgt	2112
	Ala Gly Thr Leu Thr Cys Glu Leu Lys Ser Cys Pro Tyr Cys Thr Arg	
	690 695 700	
35	gcc ctg gag gac ccg gag ggt gag ctc agc ggc tgc gaa agt gga gac	2160
	Ala Leu Glu Asp Pro Glu Gly Glu Leu Ser Gly Ser Glu Ser Gly Asp	
	705 710 715 720	
40	tca gat ggc cgt ggc gtc tat gaa ttc acg cag gac gtc cgg cac ggt	2208
	Ser Asp Gly Arg Gly Val Tyr Glu Phe Thr Gln Asp Val Arg His Gly	
	725 730 735	
45	gac cgc tgg gac ccc acg cga cca ccc cgt gcg acg gac aca cca ggc	2256
	Asp Arg Trp Asp Pro Thr Arg Pro Pro Arg Ala Thr Asp Thr Pro Gly	
	740 745 750	
	cca ggc cca ggc agc ccc cag cgg cgg gca cag cag agg gca gcc ccg	2304
	Pro Gly Pro Gly Ser Pro Gln Arg Arg Ala Gln Gln Arg Ala Ala Pro	
	755 760 765	
50	ggc gag cca ggc tgg atg ggc cgc ctc tgg gtt acc ttc agc ggc aag	2352
	Gly Glu Pro Gly Trp Met Gly Arg Leu Trp Val Thr Phe Ser Gly Lys	
	770 775 780	
55	ctg cgc cgc atc gtg gac agc aag tac ttc agc cgt ggc atc atg atg	2400
	Leu Arg Arg Ile Val Asp Ser Lys Tyr Phe Ser Arg Gly Ile Met Met	
	785 790 795 800	
60	gcc atc ctt gtc aac acg ctg agc atg ggc gtg gag tac cat gag cag	2448
	Ala Ile Leu Val Asn Thr Leu Ser Met Gly Val Glu Tyr His Glu Gln	
	805 810 815	
	ccc gag gag ctg act aat gct ctg gag atc agc aac atc gtg ttc acc	2496
	Pro Glu Glu Leu Thr Asn Ala Leu Glu Ile Ser Asn Ile Val Phe Thr	
	820 825 830	



5	agc atg ttt gcc ctg gag atg ctg ctg aag ctg ctg gcc tgc ggg cct	2544
	Ser Met Phe Ala Leu Glu Met Leu Leu Lys Leu Leu Ala Cys Gly Pro	
	835 840 845	
10	ctg ggc tac atc cgg aac ccg tac aac atc ttc gac ggc atc atc gtg	2592
	Leu Gly Tyr Ile Arg Asn Pro Tyr Asn Ile Phe Asp Gly Ile Ile Val	
	850 855 860	
15	gtc atc agc gtc tgg gag atc gtg ggg cag gcg gac ggt ggc ttg tct	2640
	Val Ile Ser Val Trp Glu Ile Val Gly Gln Ala Asp Gly Gly Leu Ser	
	865 870 875 880	
20	gtg ctg cgc acc ttc cgg ctg ctg cgt gtg ctg aag ctg gtg cgc ttc	2688
	Val Leu Arg Thr Phe Arg Leu Leu Arg Val Leu Lys Leu Val Arg Phe	
	885 890 895	
25	ctg cca gcc ctg cgg cgc cag ctc gtg gtg ctg gtg aag acc atg gac	2736
	Leu Pro Ala Leu Arg Arg Gln Leu Val Val Leu Val Lys Thr Met Asp	
	900 905 910	
30	aac gtg gct acc ttc tgc acg ctg ctc atg ctc ttc att ttc atc ttc	2784
	Asn Val Ala Thr Phe Cys Thr Leu Leu Met Leu Phe Ile Phe Ile Phe	
	915 920 925	
35	agc atc ctg ggc atg cac ctt ttc ggc tgc aag ttc agc ctg aag aca	2832
	Ser Ile Leu Gly Met His Leu Phe Gly Cys Lys Phe Ser Leu Lys Thr	
	930 935 940	
40	gac acc gga gac acc gtg cct gac agg aag aac ttc gac tcc ctg ctg	2880
	Asp Thr Gly Asp Thr Val Pro Asp Arg Lys Asn Phe Asp Ser Leu Leu	
	945 950 955 960	
45	tgg gcc atc gtc acc gtg ttc cag atc ctg acc cag gag gac tgg aac	2928
	Trp Ala Ile Val Thr Val Phe Gln Ile Leu Thr Gln Glu Asp Trp Asn	
	965 970 975	
50	gtg gtc ctg tac aac ggc atg gcc tcc acc tcc tcc tgg gcc gcc ctc	2976
	Val Val Leu Tyr Asn Gly Met Ala Ser Thr Ser Ser Trp Ala Ala Leu	
	980 985 990	
55	tac ttc gtg gcc ctc atg acc ttc ggc aac tat gtg ctc ttc aac ctg	3024
	Tyr Phe Val Ala Leu Met Thr Phe Gly Asn Tyr Val Leu Phe Asn Leu	
	995 1000 1005	
60	ctg gtg gcc atc ctc gtg gag ggc ttc cag gcg gag ggc gat gcc aac	3072
	Leu Val Ala Ile Leu Val Glu Gly Phe Gln Ala Glu Gly Asp Ala Asn	
	1010 1015 1020	
65	aga tcc gac acg gac gag gac aag acg tcg gtc cac ttc gag gag gac	3120
	Arg Ser Asp Thr Asp Glu Asp Lys Thr Ser Val His Phe Glu Glu Asp	
	1025 1030 1035 1040	
70	ttc cac aag ctc aga gaa ctc cag acc aca gag ctg aag atg tgt tcc	3168
	Phe His Lys Leu Arg Glu Leu Gln Thr Thr Glu Leu Lys Met Cys Ser	
	1045 1050 1055	
75	ctg gcc gtg acc ccc aac ggc acc tgg agg gac gag gca gcc tgt ccc	3216
	Leu Ala Val Thr Pro Asn Gly Thr Trp Arg Asp Glu Ala Ala Cys Pro	
	1060 1065 1070	
80	ctc ccc tca tca tgt gca cag ctg cca cgc cca tgc cta ccc cca aga	3264
	Leu Pro Ser Ser Cys Ala Gln Leu Pro Arg Pro Cys Leu Pro Pro Arg	
	1075 1080 1085	

5	gct cac cat tcc tgg atg cag ccc cca gcc tcc cag act ctc ggc gtg Ala His His Ser Trp Met Gln Pro Pro Ala Ser Gln Thr Leu Gly Val 1090 1095 1100	3312
10	gca gca gca gct ccg ggg acc cgc cac tgg gag acc aga agc ctc cgg Ala Ala Ala Ala Pro Gly Thr Arg His Trp Glu Thr Arg Ser Leu Arg 1105 1110 1115 1120	3360
15	cag cct ccg aag ttc tcc ctg tgc ccc ctg ggg ccc agt ggc gcc tgg Gln Pro Pro Lys Phe Ser Leu Cys Pro Leu Gly Pro Ser Gly Ala Trp 1125 1130 1135	3408
20	agc agc cgg cgc tcc agc tgg agc agc ctg ggc cgt gcc cag cct caa Ser Ser Arg Arg Ser Ser Trp Ser Ser Leu Gly Arg Ala Gln Pro Gln 1140 1145 1150	3456
25	gcg ccg gcg tgc cag tgt ggg gaa cgt gag tcc ctg ctg tct ggc gag Ala Pro Ala Cys Gln Cys Gly Glu Arg Glu Ser Leu Leu Ser Gly Glu 1155 1160 1165	3504
30	ggc aag ggc agc acc gac gac gaa gct gag gac ggc agg gcg cgc tcc Gly Lys Gly Ser Thr Asp Asp Glu Ala Glu Asp Gly Arg Ala Arg Ser 1170 1175 1180	3552
35	ggg ccc cgt gcc acc cca ctg cgg cgg gcc gag tcc ctg gac cca cgg Gly Pro Arg Ala Thr Pro Leu Arg Arg Ala Glu Ser Leu Asp Pro Arg 1185 1190 1195 1200	3600
40	ccc ctg cgg cgg ccg cct ccc gcc tac caa gtg cgc gat cgc gac ggg Pro Leu Arg Arg Pro Pro Pro Ala Tyr Gln Val Arg Asp Arg Asp Gly 1205 1210 1215	3648
45	cag gtg gtg gcc ctg ccc agc gac ttc ttc ctg cgc atc gac agc cac Gln Val Val Ala Leu Pro Ser Asp Phe Phe Leu Arg Ile Asp Ser His 1220 1225 1230	3696
50	cgt gag gat gca gcc gag ctt gac gac gac tcg gag gac agc tgc tgc Arg Glu Asp Ala Ala Glu Leu Asp Asp Asp Ser Glu Asp Ser Cys Cys 1235 1240 1245	3744
55	ctc cgc ctg cat aaa gtg ctg gtg ccc tac aag ccc cag cgg tgc cgg Leu Arg Leu His Lys Val Leu Val Pro Tyr Lys Pro Gln Arg Cys Arg 1250 1255 1260	3792
60	agc agg agg cct ggg ccc tct acc ctc tac ctc ttc tcc cca cag aac Ser Arg Arg Pro Gly Pro Ser Thr Leu Tyr Leu Phe Ser Pro Gln Asn 1265 1270 1275 1280	3840
65	cgg ttc cgc gtc tcc tgc cag aag gtc atc aca cac aag atg ttt gat Arg Phe Arg Val Ser Cys Gln Lys Val Ile Thr His Lys Met Phe Asp 1285 1290 1295	3888
70	cac gtg gtc ctc gtc ttc atc ttc ctc aac tgc gtc acc atc gcc ctg His Val Val Leu Val Phe Ile Phe Leu Asn Cys Val Thr Ile Ala Leu 1300 1305 1310	3936
75	gag agg cct gac att gat ccc ggc agc acc gag cgg gtc ttc ctc agc Glu Arg Pro Asp Ile Asp Pro Gly Ser Thr Glu Arg Val Phe Leu Ser 1315 1320 1325	3984
80	gtc tcc aat tac atc ttc acg gcc atc ttc gtg gcg gag atg atg gtg Val Ser Asn Tyr Ile Phe Thr Ala Ile Phe Val Ala Glu Met Met Val 1330 1335 1340	4032

	aag	gtg	gig	gcc	ctg	ggg	ctg	ctg	tcc	ggc	gag	cac	gac	tac	ctg	cag	4080
	Lys	Val	Val	Ala	Leu	Gly	Leu	Leu	Ser	Gly	Glu	His	Ala	Tyr	Leu	Gln	
	1345				1350					1355						1360	
5	agc	agc	tgg	aac	ctg	ctg	gat	ggg	ctg	ctg	gtg	ctg	gtg	tcc	ctg	gtg	4128
	Ser	Ser	Trp	Asn	Leu	Leu	Asp	Gly	Leu	Leu	Val	Leu	Val	Ser	Leu	Val	
				1365					1370						1375		
10	gac	att	gtc	gtg	gcc	atg	gcc	tgc	gct	ggc	gcc	aag	atc	ctg	ggt		4176
	Asp	Ile	Val	Val	Ala	Met	Ala	Ser	Ala	Gly	Gly	Ala	Lys	Ile	Leu	Gly	
				1380					1385					1390			
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	Glu Pro Gly Ile Thr Glu Gln Pro Gly Pro Arg Ser Pro Pro Pro Ser	
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	Pro Pro Gly Leu Glu Glu Pro Leu Glu Gly Thr Asn Pro Asp Val Pro	
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 1 5 10 15

Lys Met Ala

40

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/23161

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/705 C07K16/28 C12N5/10 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 04144 A (NEUREX CORP) 9 February 1995	1,2,7, 10-18, 20-22
Y	see abstract; claims 1-10 ---	3,19
X	NOONEY JM (REPRINT) ET AL: "Identifying neuronal non-L Ca <sup>2+</sup> channels - more than stamp collecting?" TRENDS IN PHARMACOLOGICAL SCIENCES, 10-1997, 18, 363-371, XP002093637 see page 369, right-hand column - page 370, right-hand column ---	1,2, 10-16, 20-22
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

16 February 1999

Date of mailing of the international search report

09/03/1999

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Gurdjian, D

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/23161

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>ERTEL S I ET AL: "Low-voltage-activated T-type Cachannels" TRENDS IN PHARMACOLOGICAL SCIENCES, vol. 18, no. 2, February 1997, page 37-42 XP004055849 see page 39, left-hand column, paragraph 4 - page 40, middle column, paragraph 1; table 1</p>	1,2, 10-16, 20-22
X	<p>----- DZHURA IO ET AL: "Characterization of hypothalamic low-voltage-activated Ca channels based on their functional expression in Xenopus oocytes." NEUROSCIENCE, FEB 1996, 70 (3) P729-38, XP002093638 UNITED STATES see the whole document</p>	1,2, 10-18, 20-22
Y	<p>----- WILSON R ET AL: "2.2 MB OF CONTIGUOUS NUCLEOTIDE SEQUENCE FROM CHROMOSOME III OF C ELEGANS" NATURE, vol. 368, 3 March 1994, pages 32-38, XP002910426 see abstract</p>	3,19
Y	<p>&amp; EMBL DATABASE Accession number q18840 WILSON R. ET AL. 1996 see the whole document</p>	3,19
A	<p>----- WO 93 04083 A (SALK INST BIOTECH IND) 4 March 1993 see abstract; claims 1-39</p>	1-22
P,X	<p>----- PEREZ-REYES E ET AL: "Molecular characterization of a neuronal low-voltage-activated T-type calcium channel 'see comments!'" NATURE, FEB 26 1998, 391 (6670) P896-900, XP002093639 ENGLAND see the whole document</p>	1-15, 20-22
P,X	<p>----- CRIBBS LL ET AL: "Cloning and characterization of alpha1H from human heart, a member of the T-type Ca2+ channel gene family." CIRC RES, JUL 13 1998, 83 (1) P103-9, XP002093640 UNITED STATES see the whole document</p>	1-22

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Information on patent family members

International Application No

PCT/US 98/23161

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WO 9304083 A	04-03-1993	US 5429921 A AU 677571 B AU 2495792 A CA 2113203 A EP 0598840 A JP 6509717 T US 5846757 A US 5851824 A US 5792846 A	04-07-1995 01-05-1997 16-03-1993 04-03-1993 01-06-1994 02-11-1994 08-12-1998 22-12-1998 11-08-1998

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